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Hyperthyroidism in the Adolescent

An Analysis of 18 Cases under 18 Years of Age[1]

[Hyperthyroidism]

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IN CONSIDERING ANY large series of patients with Graves' disease, one is invariably confronted with a few cases occurring in children and adolescents. These cases present exceptional problems in management and therapy, for the physician must consider not only the most expedient methods of treatment but every agency involved in the treatment in its relation to the normal mental and physical development of the child. Thyroidectomy has been claimed to be an undesirable procedure because, it has been said, postoperative myxedema is an all too frequent result. The consequences of such an operative misadventure have received much attention in the literature and importance has been attached to the impairment of growth and mental stunting occasioned thereby. It has also been said that postoperative recurrences are more frequent in young persons with Graves' disease than in adults. The danger that a basis for the evolution of serious behavior problems, psychoneuroses, and psychoses may be created during the period of treatment is another factor worthy of consideration. Such maladjustments of the psyche may develop only in later life under the stress of adult responsibilities, or they may appear immediately. This is particularly true if, instead of receiving the prompt, energetic, efficacious treatment which it warrants, the disease is allowed to persist in more or less active form over long periods of time during the formative adolescent age period.

Review of Literature

Several reports on Graves' disease in childhood based on collected case histories and clinical observations are to be found in the recent medical literature.

In 1926 Helmholtz (1) reported 30 cases of exophthalmic goiter in children 14 years of age or under. This figure represents all the cases of this age seen in the Mayo Clinic in a 5-year period. During the same 5-year period, 3,432 patients of all ages with exophthalmic goiter were

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observed at the clinic. There were 26 girls and 4 boys in the series. Half of the children were 10 years old or less, and symptoms of Graves' disease had been present for at least a year in more than half the cases. The manifestations of the disease closely paralleled those found in adults. The author listed the symptoms as they occurred in this series in the order of their frequency as follows:

	%
Tachycardia	100
Nervousness	93
Thyroid enlargement	93
Exophthalmos	83
Bruit	70
Increased sweating	67
Tremor	57
Weight loss	53
Polyphagia	50
Quadriceps weakness	47
G.I. disturbances	47
Dyspnea	40

In 14 cases of this group, in which the B.M.R. was determined at the time of admission, the rate varied from +11 to +55%. Upon administration of iodine the rates were reduced in all except one case. This reduction amounted to from 0 to 37%. The average reduction rate for all 14 cases was 19%. Helmholtz considered that with careful preoperative iodine preparation, one-stage operations could be safely performed in most instances. Two deaths occurred in this series. One was caused by pneumonia and one by a so-called 'postoperative crisis.' Rather low basal metabolic rates were found in all cases postoperatively, although the patients were described as normal following recovery from operation. There was no follow-up study reported, and no discussion of the possible adverse effects of thyroidectomy was included.

Twenty-six cases of Graves' disease in young people between the ages of 8 and 16 years were reported by Green and Mora (2) in 1931. Twenty-two of the patients were girls and 4 boys. One-stage subtotal thyroidectomies were performed in all instances. The symptoms and signs of hyperthyroidism were found to be essentially the same as those found by Helmholtz. These, too, closely paralleled the manifestations in the adult. In checking the blood pressures in 13 of the patients, a preoperative average of 132/65 with a pulse pressure of 67 mm. Hg was found. Following operation the average blood pressure for the same group was 108/72, with a pulse pressure of 36 mm. Hg. Weight loss was not present in 15 cases (57%). All of the patients responded to iodine, and the average preoperative B.M.R. was +34.6%. In 4 instances satisfactory clinical improvement after iodinization was noted coincidentally with an increase in the B.M.R. Following operation 5 individuals exhibited mild temporary hypothyroidism. This lasted only 6 months in the longest instance. All cases of hypothyroidism were readily controlled with small doses of thyroid substance. Twenty-one patients exhibited exophthalmos before operation. In 9 of these the eyes returned to normal after operation. Ten showed no postoperative improvement, and in 2 unilateral exophthalmos persisted. The postoperative B.M.R. varied between +14 and −30.2% with an average of −6.2%. The authors advocated in most cases a one-stage operation. They believed that less thyroid tissue should be removed in young people than in adults, without explaining their reasons therefor. In the series reported there were 4 instances of persistent or recurrent hyperthyroidism. Two of these improved on iodine, and 2 required a second operation. All 4 were reported as cured after varying time intervals following the recurrence of symptoms. No deaths occurred in this series.

Dinsmore (3) in 1932 made a somewhat similar study of 57 cases of Graves' disease in children under 14 years of age. The frequency of occurrence of the various symptoms of the disease found in his series closely parallels that of Helmholtz. Dinsmore considered the principal contributing factors to Graves' disease in children to be hereditary, racial, and infectious. Iodine administered prophylactically was not thought to influence the incidence of the disease in children. Thyroidectomy gave gratifying results. Adequate preparation for operation was found to be most important. Attention was called to the necessity of leaving enough thyroid tissue at the time of operation to supply normal needs, and the author warned against the danger of postoperative hypothyroidism if this was not done. It was his impression, after following some of the cases through high school and college, that they were perfectly normal individuals except for occasional instances of mild, transient hypothyroidism. Of the 57 cases discussed, 43 were subjected to operation. Two deaths occurred. There was no mention of any case in which a severe degree of myxedema developed postoperatively.

In 1935 Bloom (4) described 40 cases of hyperthyroidism in children. All of these were treated conservatively over long periods of time. Treatment included rest, proper food (containing iodine), and attention to hygiene and water balance. Varying amounts of Lugol's solution were given each patient. In his experience radiotherapy and surgery were not necessary in any case. It was pointed out that early recognition of the symptoms of Graves' disease was important in order to avoid subsequent operative procedures.

Lehman (5) in 1936 reported 6 cases of hyperthyroidism in children from 4 to 14 years of age. By comparing the figures advanced by various authorities, he estimated the incidence of childhood Graves' disease to be about 1 in each 100 cases of the disease as it occurs in persons of all ages. In discussing the etiological aspects, he found an hereditary factor in 50% of the cases. In one instance, there was associated hypopituitarism. Other endocrine disorders were not found. The author stated his belief that neither iodine nor infection caused hyperthyroidism but that the latter definitely augmented the condition. In his cases physical overdevelopment and sexual precocity were striking findings. The onset of symptoms of Graves' disease was described as quite abrupt, averaging 6 months before recognition. He found that with exophthalmos of one year's duration or more, little regression could be expected with any mode of treatment. For diagnostic purposes a therapeutic trial with iodine was considered important. This author disapproved of any trial of conservative measures because he thought it unfair to both patient

and doctor to await an exacerbation of symptoms before proceeding to operation. It was his opinion that less gland should be removed from children than from adults. He took this view because of the danger of inducing hypothyroidism in growing children. No direct evidence to support the actuality of such a danger was given. After operation his cases were followed for periods of 11 months to 3 years. All 6 were described as cured.

In 1937 Bram (6) reported 128 cases of exophthalmic goiter in children 12 years of age or under. He found that these 128 children suffering from Graves' disease constituted 2.5% of about 5,000 instances of Graves' disease in patients of all ages seen over a period of many years. Only 8 children in the entire group of 128 were males. In 50% of the cases he found a related infection in teeth, tonsils or both. General infection was found to be an etiological factor in 22%, a preexisting simple goiter in 12%, and psychic trauma in 6%. Goiter and exophthalmos were said to have occurred in 90% of the cases and bruit in 65%. Gastrointestinal symptoms were found to have been more intense and more frequent than in adults. Less weight loss was noted than in adults. Undue augmentation of height in children approaching 11 years was frequently found. Other symptoms were essentially the same as in adults. Bram emphasized in his discussion the need of conservatism in the treatment of childhood Graves' disease in order to conserve the thyroid gland, as "children may easily be transformed into pseudocretins by thyroid ablation." He advocated "medical therapy" without operation in most cases but admitted that expert surgery and radiation have a distinct value in a "certain percentage of cases." No figures or conclusive statements as to the ultimate results in these "medically treated" cases were given. No instances of pseudocretinism following operation were cited. Medical therapy as suggested included removal of infections, an adequate diet without excess carbohydrate because of a deficiency in carbohydrate metabolism, a diet low in animal protein, keeping the patient in bed most of the time, psychotherapy, and drugs. The drugs suggested as being useful were sajodin (iodine) in minimal doses, quinine, eserine salicylate, and barbiturates. He advised care in the administration of iodides, stating that "if any doubt exists relative to their use in a given case it is far better not to employ them at all than to take chances." The author went on to say that in his series "an occasional instance of exophthalmic goiter was said to have followed iodine medication for simple goiter. There are many individuals, young and old, who are iodine sensitive and easily made iodine-fast."

In 1937 Beilby and McClintock (7) discussed hyperthyroidism in children. These writers, with an experience of 8 cases under the age of 14, considered nonoperative treatment much more dangerous in the child than in the adult because of the developmental factor. They found in their cases striking evidence of precocious skeletal development at the expense of soft tissue development. A case of one year's duration was reported in which a child, 2¾ years of age, showed marked cardiac enlargement. This same child at the age of 4 had the skeletal development of a child of 9 as determined by x-ray. These writers maintained that it is difficult to be too radical in performing thyroidectomies on children because the thyroid gland in the child regenerates so much more rapidly than in the adult.

In 1937 Crile and Crile (8) described 4 cases of hyperthyroidism in children under 5 years of age. Prominent eyes were present in all of the cases, and the symptoms evidence a severe form of the disease. In the first case rest and iodine were prescribed. As the child failed to return to the clinic the case could not be followed further. A second case underwent subtotal thyroidectomy after failing to respond to hospitalization and iodine. Following operation, the hyperthyroidism persisted and exophthalmos became more pronounced. A second thyroidectomy and left adrenal denervation, performed 3 months after the first procedure, induced lasting improvement, although the exophthalmos grew progressively worse for a time postoperatively. A third child failed to improve after x-ray therapy to the thymus and the thyroid gland. Hospitalization, iodine, and sedation were prescribed for 10 days after which a 3-stage operation was performed. Good results were noted 18 months later. A fourth individual with very severe symptomatology underwent subtotal thyroidectomy after 12 days' preparation. The patient was said to be improved several months later. In their discussion the authors remarked that exophthalmos, more common in children than adults, was often severe and might not recede postoperatively. They considered it to be of the greatest importance to follow the eyes closely in all cases of Graves' or suspected Graves' disease because they found that an early adequate operation usually prevented exophthalmos. The authors did not find conservative treatment satisfactory but said that in mild or very early cases it might, with close observation, be tried. They felt that operation in the child was as successful as in the adult and saw no reason to make the child an invalid in order to carry out conservative measures of treatment. In 40 cases under 14 years of age in which iodine was used preoperatively, the authors had no operative fatalities. They considered a 1-stage operation after iodinization to be a satisfactory procedure.

In 1938 Atkinson (9) reported an analysis of 208 cases of Graves' disease in children of 14 years of age or less. The cases were collected largely from the European literature. Tachycardia was found to be the commonest symptom. Thyroid enlargement occurred in 97% of these individuals, and exophthalmos was noted as having an incidence of 75 to 84%, according to the method of computation. Tremor was noted in 80% of the cases. Symptoms were found to appear more suddenly and to develop more rapidly in children than in adults. Infections, psychic upsets, and heredity were important etiologically. Eighty per cent of the cases were in girls. The incidence of the disease increased with the age. In the entire series only 6 deaths occurred. One of these patients had a large thymus. Atkinson stated that the prognosis in children was better than in adults. He advised treatment as for adults but said that thyroidectomy was to be performed with caution for fear of subsequent hypothyroidism. Again there was no discussion of any specific instances in which serious postoperative hypothyroidism occurred, although according to his tabulation 4 individuals de-

veloped questionable hypothyroidism. It was not stated whether operation was performed on these cases or not.

Welti (10) in 1938 discussed 24 cases of severe Graves' disease in children less than 17 years of age. Exophthalmos was marked in more than one-third of his cases. Early operation for this reason seemed to him to be advisable in an effort to lessen the degree of the exophthalmos. The frequency of juvenile Graves' disease, unaccompanied by marked malnutrition, was considered a matter of note by this writer. He found skeletal development to be accelerated, advanced ossification being a characteristic x-ray finding. The effect on dentition was particularly disturbing. Replacement of the milk teeth was noted at the age of 3½ years in one case, and at 5 years the child's dentition was that of a 9-year-old. Faulty alignment and retraction of the upper jaw on the lower was present. Not only was precocious skeletal development observed but also defective calcification. The broad effects of hyperthyroidism on intellectual development were also found to be adverse. In girls the establishment of regular menses was notably delayed. If menstruation was already established the periods usually became irregular or diminished in amount. At times they ceased entirely. In boys the testicles remained small and the development of pubic and axillary hair was retarded. Severe cardiac manifestations were present less often. Operations at least as radical as in adults were found necessary to obtain lasting cures. In 2 cases in which operations less radical than the customary subtotal thyroidectomy were performed, improvement was quite transitory. The author stated: "It is exceptional to observe in children the transitory phenomena of hypothyroidism which are relatively frequent following intervention of the same degree in adults." In only 1 of the 22 children undergoing extensive resections was there any evidence of hypothyroidism. In this instance, the hypothyroidism was mild and disappeared rapidly. This low incidence of postoperative hypothyroidism was interpreted as showing that following subtotal thyroidectomy small amounts of thyroid tissue hypertrophy more readily in children than in adults. Finally, the author concluded that operation was quite as definitely indicated in the child as in the adult and could be expected to yield, in general, even better results.

Gould and Robertson (11) reported in 1938 thyroidectomy in a severe case of Graves' disease occurring in a child of 4 years. The basal metabolic rate initially was +40%. After 3 months of treatment without iodine the child had become worse. Iodine was then administered with dramatic response, and a thyroidectomy was performed. After 18 months the disease recurred. A second operation in which all grossly visible thyroid tissue was removed was done 3½ years after the first procedure. The patient was subsequently followed for 3 years and found to be normal in every respect. The authors stated their belief that if the patient was carefully prepared with iodine, a 1-stage removal of seven-eighths of the thyroid gland was safe and desirable even in young children.

Klapper (12) in 1939 described thyroidectomy on a male child 5 years of age for very severe exophthalmic goiter. Preoperative iodine therapy was found ineffectual. Subtotal thyroidectomy was performed in 3 stages. The patient convalesced uneventfully and was followed for 10 months after the operation. He was entirely normal in his growth, muscle strength, and social reactions during the follow-up study, and his mental status was said to have been markedly improved.

PRESENT STUDY

The study herewith reported was undertaken primarily in an effort to evaluate the results of the various methods of treatment employed in the New York Hospital in the handling of Graves' disease in children. It was hoped that some common denominator which might serve as a basis for therapeutic endeavor would result from such a study. The problem as to whether it is best to perform subtotal thyroidectomy as soon as the patient has received the necessary preoperative preparation or to attempt to carry pre-adult patients on a so-called 'medical regime' in the hope that with the passage of time the disease will subside has been a vexing one. That there are various schools of thought on the matter is brought out in the review of the literature cited above. Bram (6) stressed the need of conservatism in the treatment of Graves' disease in childhood to preserve the thyroid gland and avoid pseudocretinism, while Welti (10) concluded that operation in the child is as definitely indicated as in the adult and can be expected to yield even better results.

As will be readily understood the difficulties inherent in a study of this kind make highly statistical analysis impossible. It seemed reasonable, however, that with the follow-up study available in most of the cases a consideration of such factors as total preoperative duration of the disease, mental and physical development during the long-continued periods of hyperthyroidism often seen in a conservative regime, and psychic maladjustments incident to the enforced invalidism of prolonged nonoperative treatment might be productive of some conclusions as to how such cases may best be handled.

The material on which this study is based was drawn from the case records of the New York Hospital. The term Graves' disease is used in this paper to represent all patients with the symptoms of hyperthyroidism. During the period from Sept. 1, 1932, to Sept. 1, 1940, 747 patients of all ages with toxic goiters, either diffuse or nodular, were seen in the New York Hospital on the medical, surgical, and pediatric pavilion services. There were 465 instances of toxic diffuse goiter and 282 cases of toxic nodular goiter. Twenty-six of the 747 patients were under 18 years of age. Accordingly, 3.5% of all patients with Graves' disease seen in the hospital during the past 8 years were children under 18 years of age. These figures do not, of course, give any notion of the incidence of the childhood form of the disease as it occurs

in the population at large but they do afford some indication of the relative infrequency of the disease as seen in hospital practice. Eighteen of the 26 individuals mentioned above were patients of the medical and surgical services and constitute the group utilized in the present study. Seventeen of the 18 had toxic diffuse goiters, and 1 had a toxic nodular goiter. One of the 18 members of the series was first seen with a recurrence of Graves' disease after having undergone subtotal thyroidectomy elsewhere 18 months previously. The other cases were all seen before any operative procedure had been carried out.

RESULTS

The group of cases studied was composed of 15 girls and 3 boys. The ages of the patients ranged from 10 to 17 years at the time of onset of symptoms. The estimated ages at the time of onset of symptoms are tabulated in table 1.

TABLE 1. APPROXIMATE AGE OF ONSET OF SYMPTOMS

Age in years	10	12	13	14	15	17
No. cases	1	1	5	8	1	2

It is of interest to note that in 13 cases, or 72% of the entire series, the onset of symptoms occurred at the 13 and 14-year age level. Eleven of these 13 cases were girls. It is at approximately this age, according to figures given by Engle and Shelesnyak (13) based on a study of 250 girls in the Hebrew Orphan Asylum of New York City, that menarche usually occurs. They found the average age at menarche for their group to be 13.5 years.

The patients in this study were all white children of varied racial extraction. Etiological factors involved include histories of: *a*), infection, either closely preceding or associated with the appearance of symptoms in 3 cases (17%); *b*), psychic trauma in 5 (28%); *c*), Graves' disease or "goiter trouble" in parents or close relatives in 6 (33%); and *d*), combinations of two of these factors in 3 patients (17%).

In only one case was there association with another endocrine disorder; *case* 9, a boy of 14, showed signs of hypogonadism.

Histologically all glands resected, with one exception, were described by the surgical pathologist as "hyperplastic goiters" showing various degrees of involution. The solitary nodule resected in the one exception, *Case* 6, was described as an "intermediate adenomatous goiter (fetal adenoma)." The symptomatology in this patient was entirely similar to that of the other cases although no exophthalmos was present.

PRESENTING ASPECTS OF THE DISEASE

The presenting features of the disease as recorded at the time of the patients' admission to the New York Hospital are summarized in table 2. *Case* 15 is not included in some of the percentage figures as she was first seen with a recurrence of symptoms following thyroidectomy elsewhere. Percentages are based

TABLE 2. SUMMARY OF SYMPTOMS, SIGNS AND LABORATORY FINDINGS ON ADMISSION

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15[1]	16	17	18
Age of onset (yr.)	12	13	14	14	17	14	13	15½	14	14	10	13½	14	13½	14	17	14	13
Nervousness	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Appetite	+		+	+	+	o	o	+	+	+	+	+	+	+	−	+	−	
Body weight	−	o	−	+	−	o	−	−	−	o	−	o	−	−	−	−	−	o
Weakness	−	+			−	+		+						−	+	+	+	
GI disturbances	−	−	−	+	−	−	−	+	−	−	−	−	+	−	+	−	+	−
Dyspnea	−	−	−	−	−	+	+	−		+	−	−	+	−	+	+	+	
Pulse	132	128	128	100	130	115	140	124	110	128	120	100	128	130	108	146	130	120
Thyroid enlargement	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Exophthalmos	+	−	−	+	+	−	+	+	−	+	−	+	+	+	+	−	−	+
Bruit	+	−	+				+	+	−	−	−	−	+	+	+	+	+	+
Sweating	+		+	+	+	+	o	+	+	+	+	+	+		+	+	+	+
Tremor	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood pressure	130	138		140	135	130	142	148	140	154		129	160		130	140	155	175
	65	56		50	58	68	74	68	50	70		62	60		68	65	80	60
B.M.R.	+79	+25	+30	+52	+57	+35	+30	+66	+35	+25	+30	+26	+54	+38	+25	+38	+57	+27
Blood cholesterol			140	170				161	196						130			
W.B.C., thousands			9.3	5.5	4.0	10.8	8.9	5.1	7.4	7.2	10.8	9.5	12.6	7.0	13.9	8.2	7.0	7.3
% lymphocytes			51	26	19		37	52	28	33	25	27	18	42	38	32	17	51

[1] Patient 15 was first seen with a postoperative recurrence. In the text the percentage figures include *case* 15 for all symptoms and laboratory findings except blood pressure, B.M.R., blood cholesterol and W.B.C. counts.

+ indicates symptom was present or item was increased above normal. − indicates symptom was absent or item was subnormal. o indicates normal or stationary condition.

on the number of cases for which each symptom, sign, and laboratory finding was recorded.

Nervousness was present in 17 cases or 100%. Increased appetite appeared coincidentally with the onset of symptoms in 12 instances. The status of the appetite was not recorded in 2 cases. In 2 the appetite remained normal, and in 2 others either poor appetite or loss of appetite was noted. Body weight decreased in 12 cases, including *case 15*. Weight loss associated with polyphagia occurred in 9 instances. Loss of weight associated with a poor appetite or loss of appetite occurred in 2 individuals. In 2 others exhibiting polyphagia the weight remained stationary.

TABLE 3. SUMMARY OF BLOOD PRESSURES

Preoperative averages			Postoperative averages		
Syst.	Diast.	Pulse	Syst.	Diast.	Pulse
	mm. Hg			*mm. Hg*	
130	68	62	—	—	—
139	69	70	128	84	44
131	70	61	118	74	44
132	61	71	—	—	—
139	62	77	111	68	43
130	68	62	112	69	43
142	74	68	—	—	—
134	64	70	—	—	—
131	58	73	105	72	33
135	62	73	—	—	—
—	—	—	97	62	35
125	63	62	—	—	—
160	60	100	113	72	41
116	58	58	—	—	—
140	72	68	133[1]	65[1]	68[1]
166	61	105	120	90	30
138	67	71	107	67	40
Mean					
137	65	72	112[2]	73[2]	39[2]

[1] With recurrence.
[2] Recurrence omitted in average.

In one instance polyphagia was associated with a gain in weight, and in another both weight and appetite remained more or less normal. Weakness, unqualified, was listed 6 times. In the other cases the symptom was absent or not mentioned.

Gastrointestinal disorders, including abdominal pain, nausea, vomiting, and diarrhea occurred in 5 instances (33%). Exertional dyspnea was recorded in 7 of the 18 cases. The pulse rate was 120 or more in all except 5 individuals. In no case was the rate less than 100.

Enlargement of the thyroid gland was present in all except 1 of the 18 children (94%). In the case of the one exception enlargement developed after 3 months of iodine therapy. Exophthalmos was present in 11 of the 18 cases (61%). In 6 of the 7 showing no exophthalmos when first seen, some degree of proptosis subsequently developed. This sign developed in 2 individuals during protracted conservative treatment in which iodine was administered. In 2 others it developed in the course of postoperative recurrences, and in 2 it appeared postoperatively in the absence of a recurrence of toxic symptoms. A bruit was present in 10 of the 15 cases in which the sign was recorded (67%). Hyperidrosis was present in 15 of 16 instances (94%) in which the sign was mentioned. Tremor occurred in 17 of the cases (94%).

The blood pressure findings are summarized in table 3. Systolic and diastolic levels both before and after operation represent, as recorded, averages of several determinations. All recorded readings were averaged in each case except in those instances in which readings were particularly numerous and at approximately the same levels. The preoperative readings were used without consideration for iodine administration and its altering effect on the manifestations of the disease. The postoperative averages include readings made over considerable periods of time following convalescence and are by no means confined to intervals in which postoperative asthenia was persistent. When the figures for preoperative and postoperative systolic and diastolic blood pressure levels are averaged it will be noted that the preoperative systolic level of 137 mm. Hg was considerably higher than the postoperative level of 112 mm. Hg. The preoperative diastolic level of 65 mm. was significantly lower than was the postoperative level of 73 mm. Hg. If the postoperative levels be considered as the normal, then it becomes apparent that not only was the systolic blood pressure elevated in the presence of Graves' disease, but also there was a significant lowering of the diastolic level. This alteration in blood pressure is particularly well seen by comparison of the pulse pressures preoperatively and postoperatively. Expressed in percentages the average systolic reduction following operation amounted to 18% of the preoperative level. The diastolic level increased 13% of the preoperative level, and the pulse pressure was reduced by 46% of the preoperative figure following thyroidectomy. The factors influencing blood pressure in Graves' disease have been discussed by various writers (14–18). The interrelationship of these factors and the precise mechanism involved in producing the changes found are necessarily of a complex nature. The systolic elevation and diastolic depression found in the disease as seen under clinical conditions are, however, immediately effected for the most part through pathological-physiological factors whose total effect increases the cardiac output on the one hand and decreases peripheral resistance on the other.

The B.M.R. varied from +25 to +79% on admission with an average of +40.5% for the 18 cases. Blood cholesterol determinations according to the modified method of Bloor (19, 20) were made near the

time of admission in some instances. The readings in individual cases varied from 140 to 196 mg. %. Determinations of questionable accuracy because of possible postprandial alteration were not included in the tabulation. The average of 4 determinations was 167 mg. % (table 2). As the normal range of values determined by the method in use is 175 to 225 mg. % it was apparent that cholesterol determinations had little diagnostic value in this series of cases of Graves' disease.

In the present group 14 patients, seen preoperatively, had routine admission leucocyte and differential counts recorded. The total leucocyte count varied from 4,000 to 12,600 cells per cu. mm. of blood and averaged 7,843. The lymphocyte count expressed in percentage of the total leucocyte count varied from 17 to 52 and averaged in 14 cases was 32.6. The absolute lymphocyte count varied from 760 to 4,743 cells per cu. mm. of blood and averaged 2,509. No correlation between the severity of the disease and the degree of lymphocytosis was apparent. There was no relationship observed between the estimated duration of symptoms of Graves' disease at the time of admission and either the percentage or absolute number of lymphocytes (table 4).

TABLE 4. SUMMARY OF ROUTINE ADMISSION LEUCOCYTE, LYMPHOCYTE, AND B.M.R. FINDINGS

Case	Estimated Duration of Symptoms	Leucocytes	Lymphocytes		Adm. B.M.R.
	mo.	*/mm.³*	*%*	*/mm.³*	
5	1.5	4000	19	760	+57
16	3	8200	32	2624	+38
4	3	5500	26	1430	+52
11	4	10,800	23	2484	+30
8	4	5100	52	2652	+66
9	4	7400	28	2072	+35
3	5	9300	51	4743	+30
14	6	7000	42	2940	+38
10	7	7200	33	2376	+25
17	8	7000	17	1190	+57
7	12	8900	37	3293	+30
12	18	9500	27	2565	+26
13	25	12,600	18	2268	+54
18	12	7300	51	3723	+27
Averages		7840	33	2509	+40

In view of the fairly prevalent belief that an increased lymphocyte count is found in the peripheral blood stream in cases of Graves' disease, this point was examined with some care. When the above figures were compared with those reported in a series of studies recently published by Osgood and his associates (21, 22, 23) no evidence of any increase in lymphocytes, using their figures as representative of normal values, could be found. On the contrary the averages for the total leucocyte count, percentage number of lymphocytes, and absolute number of lymphocytes were well below the normal averages found by those workers in all instances (see table 5).

The lymphocyte findings are in fairly close accord with those published by McCullagh and Dunlap (24). They found that in 250 differential counts in cases of hyperthyroidism the average relative number of lymphocytes was 30.3% and the average absolute number of lymphocytes 2,412.3. Little or no relationship between the severity of the Graves' disease and the percentage of lymphocytes per cu. mm. of blood was found. The relative number of lymphocytes appeared to bear a close relationship to the total leucocyte count and especially to the absolute number of polymorphonuclear leucocytes in their series. They concluded that, since there was a relative lymphocytosis of 30% or above in 60% of the large series of hyperthyroid cases, the presence of a lymphocytosis was of some diagnositic value. This despite the fact that the absolute number of lymphocytes remained fairly constant with respect to the severity of the disease.

TABLE 5. ROUTINE ADMISSION LEUCOCYTE AND LYMPHOCYTE FINDINGS COMPARED WITH NORMAL VALUES

	Normal Values[1]		Present Study
	8–14 yr.	15–18 yr.	10–18 yr.
Leucocytes/cu. mm.	8400	8400	7843
95% Range	4000–13,000	4000–13,000	4000–12,600
Lymphocytes %	48	42	32.6
95% Range	20–70	22–62	17–52
Lymphocytes/cu. mm.	4000	3250	2509
95% Range	1500–6500	1500–5000	760–4743

[1] From Osgood, et al. (21, 22, 23).

General Care and Treatment

All patients whether managed with or without recourse to operation were put on a regimen including increased rest, usually bed rest for at least part of the time, a high caloric diet, sedation, and iodine. An attempt was made in most instances to evaluate the psychological background of the individual and alleviate such adverse environmental factors as were present. Iodine was given in various forms, usually as syrup of hydriotic acid or Lugol's solution, and in various dosages, continuously or intermittently. When surgery was postponed, the patients were handled in several ways; *a*), observed in the hospital for long periods of time, *b*), sent to convalescent homes and camps in an effort to improve their surroundings, or *c*), followed at frequent intervals in the Thyroid-Endocrine Clinic of the hospital. The Social Service and psychiatric agencies associated with the

hospital cooperated freely in an effort to improve home conditions and secure a better adjustment of the individual to his environment.

Management (with Reference to Operation)

From the standpoint of operation patients were handled in three ways.

Group 1. Subtotal thyroidectomy within 60 days after the institution of iodine therapy. There are 9 cases in this group (*Cases 1, 3, 5, 6, 7, 11, 16, 17, 18*). The results of operation are given in table 6. Six cases enjoyed a smooth and uneventful postoperative course and were considered entirely normal developmentally when seen during the follow-up studies.

TABLE 6. RESULTS OF SUBTOTAL THYROIDECTOMY WITHIN 60 DAYS AFTER THE INSTITUTION OF IODINE THERAPY

Physical Status			Mental Status
Clinical Cures	Recurrences	Myxedemas	Maladjustments
Cases 1, 3, 5, 6, 7, 11	Cases 16, 17[1]	Case 18[2]	Case 17
Totals 6	2	1	1

[1] Persistent hyperthyroidism
[2] Transient

Records of basal metabolism and pulse indicated that these cases were of average severity. In no instance was there any mention of the appearance of behavior problems or psychic maladjustments; these boys and girls have lived normal, active lives, participating in the usual athletic, social, and educational life common to children of their own age.

One case had a recurrence of symptoms and another exhibited signs of persistent hyperthyroidism following operation. One of these two in whom the disease persisted over a long period of time became maladjusted and presented a behavior problem. One patient developed a mild, transient postoperative myxedema.

Group 2. (a) Conservative treatment in excess of 60 days' iodinization without subsequent thyroidectomy. In this group there are 2 cases. Their general care and treatment has been discussed above. Summaries of the clinical courses of these 2 individuals follow.

Case 14, a girl 14 years old, with moderately severe Graves' disease, responded well to iodine and conservative measures after admission to the hospital. After 97 days of hospital treatment she was discharged and got along satisfactorily for about 1 year. She then suffered a recurrence of her hyperthyroidism. Operation was recommended but refused. She was followed in the Thyroid-Endocrine Clinic for 2 years in a state of chronic hyperthyroidism. No signs of any psychological maladjustment developed during that period. The patient subsequently failed to return to the clinic and has not been seen for the past 2 years.

Case 12, a 14-year-old girl, with a relatively mild case of Graves' disease, was admitted to the metabolism ward of the New York Hospital and followed for 100 days therein. She received the usual supportive treatment as outlined elsewhere. Iodine was administered both in the hospital and after discharge over a period of 2 years. This patient responded well to conservative measures and was physically normal and mentally balanced 4 years after the onset of her disease.

(b) Conservative treatment in excess of 60 days' iodinization with subsequent thyroidectomy because of failure of non-operative therapy. In this group there are 6 cases (*Cases 2, 4, 8, 9, 10, 13*). The postoperative findings are listed in table 7. All 6 of these cases from a physical standpoint enjoyed either smooth and uneventful postoperative courses or experienced minor disturbances which readily cleared after a period of a few months. The degree of toxicity on admission was essentially the same as in *group 1*. It must be realized, however, that the 60-day period chosen as the dividing line between cases undergoing immediate operation and cases subjected to a conservative regimen in the hope of cure without operation necessarily sets up an artificial and inaccurate grouping. With this fact in mind it becomes apparent that several of the most severe cases on whom operation at the earliest date consistent with adequate preparation was manifestly planned from the time of admission are included in *group 2 (b)*. Preparation in excess of 60 days' iodinization was considered wise in these severe cases by those in charge. Consequently, according to the manner of division, such cases are wrongly grouped. When they are removed from *group 2 (b)*, 4 cases (*Cases 2, 4, 9, 10*) remain for consideration. These 4 patients therefore comprise the group in which surgical intervention was purposely postponed following, in all instances, a prompt and dramatic response to iodine therapy and hospital management. It was the hope of those responsible that the marked improvement noted after conservative treatment represented a cure and that operation

TABLE 7. RESULTS OF CONSERVATIVE TREATMENT IN EXCESS OF 60 DAYS' IODINIZATION WITH SUBSEQUENT THYROIDECTOMY BECAUSE OF THE FAILURE OF NON-OPERATIVE THERAPY

Physical Status			Mental Status
Clinical Cures	Recurrences	Myxedemas	Maladjustments
Cases 2, 4, 8, 9, 10[1]		Case 13[2]	Cases 2, 4, 13
Totals 5	0	1	3

[1] No follow-up
[2] Transient

would prove unnecessary. This hope did not materialize, however, and after conservative methods of treatment had been employed for periods of time varying from 9 months to 4 years 7 months, operation became necessary.

The average B.M.R. on admission for this group of 4 cases was 34%, a figure only slightly lower than that for the entire group. This would apparently indicate that the toxicity of the cases when first seen had little to do with the decision as to whether operation should be done immediately following preparation or dismissed in favor of conservative therapy.

DISCUSSION

The wisdom of these various programs of management and treatment in the light of the results must next be examined. The important points are stated as questions for the sake of emphasis. (*a*) Is it desirable or undesirable to maintain pre-adult patients on a so-called 'medical' regime without operation? (*b*) Can conservative treatment alone produce a cure? (*c*) Does the maintenance of a prolonged state of subacute hyperthyroidism as is so often seen in unoperated patients, militate against the normal growth and development of the child? (*d*) Are extended periods of supervision with the restrictions, often amounting to invalidism, incident thereto prejudicial to the child's best interests? (*e*) Does thyroidectomy during the formative years jeopardize normal development by causing a deficiency of thyroid substance? If so, should this consideration outweigh the disadvantages of conservative therapy? (*f*) Are recurrences more frequent and operative mortality rates higher in young people than in adults? (*g*) Is it possible to maintain a high percentage of cases of childhood Graves' disease on a nonoperative regime without recourse to surgery? The answers to these crucial questions as revealed by this study are incorporated in the discussion to follow.

Failure of Conservative, Non-Surgical Treatment Alone to Produce Permanent Arrest of the Disease

When the 6 patients in *groups 2* (*a*) and 2 (*b*) receiving iodine therapy in excess of 60 days and in whom thyroidectomy was purposely postponed are considered, it may be noted that in every instance a prompt and satisfactory response to iodine, sedation, diet and bed rest occurred. In 5 of these cases, however, symptoms of hyperthyroidism either persisted to some extent or recurred after longer or shorter periods of time. When the patients in *groups 2* (*a*) and 2 (*b*) are individually considered, the failure of conservative measures of treatment is quite striking. One patient with a recurrent Graves' disease has been lost to the hospital, and 4 individuals have undergone thyroidectomy. The sixth member of the group has apparently obtained a nonoperative cure. The percentage of failure to cure by conservative measures of treatment alone in 5 of 6 cases so handled is, accordingly, 83%.

Ill Effects of a Prolonged Period of Conservative Treatment on the Psychic Balance of the Individual

Three of the 6 cases treated with iodine for periods longer than 60 days prior to operation, including both those cases purposely maintained on a prolonged conservative regimen and those requiring more than 60 days of iodinization for adequate preparation, have developed manifest behavior problems of one sort or another (see table 7). The 2 patients in *group 2* (*a*) whose treatment was conservative and prolonged developed no definite psychic problems, although one was in a chronic hyperthyroid state and emotionally unpredictable when last seen.

If, however, the 2 cases in *group 1* which developed recurrences or had persistent hyperthyroidism following early operation plus *case 15* (a case first seen in the New York Hospital with a recurrence of Graves' disease) are considered from the viewpoint of a psychic upset, it is noteworthy that 2 of these 3 individuals developed some form of mental maladjustment. This last group is, of course, quite comparable to *group 2* (*b*) as regards the development of maladjustments in that its members were subject to restrictions, and supervisions, incident to their recurrences, in the same manner as were individuals treated with conservative measures for prolonged periods preoperatively. The percentage of cases developing maladjustments in the combined group of those treated for prolonged periods was 55. When one considers that this figure represents only those cases which have evidenced maladjustments of the psyche sufficiently pronounced to merit notes in the charts, he can realize that psychical insults less overt in their manifestation are undoubtedly sustained in the course of prolonged illnesses during childhood. With this thought in mind, no one should deny that the duration of the illness should be made an extremely important consideration in determining the type of treatment to be used in juvenile Graves' disease.

The fact that two-thirds of the total number of cases developing problems of psychic adjustment occurred in children whose chance for a prompt postoperative recovery following operation early in the course of the disease was foregone in a futile effort to cure conservatively speaks for itself. This point is further emphasized when one realizes that 50% of all cases in which operation was delayed only to be performed subsequently developed behavior prob-

lems. This finding is in marked contrast to the low percentage (11%) of patients developing behavior problems in the group operated on within the 60-day period of iodine preparation. When one considers that this 11% incidence of maladjustment in the latter group derives solely from one case suffering a prolonged illness by reason of repeated recurrences and that in no case in which uneventful recovery occurred did psychic problems arise, the contrast is even more striking. It is a reasonable assumption that fewer recurrences will be encountered following early operation than psychic maladjustments incident to expectant treatment.

It is impossible to estimate the dangers pursuant to the institution of personality changes, no matter what the source may be, in a human life during the formative years. Children are undoubtedly markedly susceptible to environmental factors which influence more mature individuals but little. The character and personality of the child is so completely pliant and labile that its responses are out of all proportion to the applied stimulus. The effects of environmental factors are readily measurable on young and old alike by such relatively gross objective criteria as growth, muscular development, and nutrition. Yet these same gross criteria clearly reveal that environment influences the growing young person to a much greater extent that it does those fully developed in mind, habits, and physique. By the same token one can only surmise how immeasurably greater are the effects of an adverse mental environment on the plastic personalities of children. There is no satisfactory yardstick whereby such intangible values in cause and effect can be estimated, yet those who are experienced in child welfare or who have had occasion to examine the backgrounds of juvenile delinquents can produce a wealth of material showing that the early development of such individuals has taken place, in an extremely high percentage of cases, in an environment of spiritual, moral, and social disorder. What the factors involved are and how they work to set the human personality astray, it is not within the province of this discussion to say. The prolonged invalidism consequent to the watchful waiting of conservative treatment in juvenile Graves' disease can represent such a factor, and should be regarded as such. Children kept from school, kept from play with their comrades, and made objects of sympathy and even pity by their elders do not enjoy a healthful mental environment conducive to the normal growth and development of the human personality.

Other Disadvantages of Prolonged Non-Surgical Treatment in Juvenile Graves' Disease

Cost. Prolonged medical therapy is costly. The patient often requires hospital admission not only for a thorough-going analysis incident to diagnosis but also for prolonged treatment under controlled conditions wherein progress may be closely followed. The group treated conservatively in this series averaged more hospital days per patient than did the group subjected to operation as soon as preparation was adequate. In addition to an increase in hospital charges and physicians' fees, the cost to the family incident to invalidizing such children at home for long intervals of time is incalculable.

Schooling. Home-treated hyperthyroid cases, with the interruptions of sporadic hospitalization and recrudescences of symptoms occurring from time to time, usually fall behind in school for from 6 months to 2 years as judged by hospital records. Even if the disease is considered mild enough to permit of fairly regular school attendance, the sick child usually lags because of an inability to concentrate. He thus becomes abnormal in his own estimation in that he cannot keep pace with his fellows. Such an attitude may readily constitute a factor in the genesis of a behavior problem.

Control of Patients. All too frequently the attending physician prescribes for the young hyperthyroid patient rest, sedation, adequate diet and iodine only to find on a follow-up visit that his patient "just wouldn't do as he was told." The parents profess an inability to control the child and the latter goes untreated. Another hazard encountered is the moving of families from the physician's sphere of activity. The young patient fails to see another physician and may experience a flare-up of his trouble with, at times, actual danger to life.

Exophthalmos. As mentioned earlier, exophthalmos was present in 61% of the children in this series at the time of admission to the hospital. In several instances frank exophthalmos subsequently developed during the period of observation while the patient was receiving treatment. In other cases a suggestive widening of the palpebral fissures appeared. When those cases developing eye signs during the period of observation and treatment are added to those exhibiting exophthalmos at the time of admission, suggestive findings are found to have developed in 94% of the cases at some time during the course of the disease. In several instances, however, this 'borderline' exophthalmos was apparently a transient phenomenon, disappearing entirely within the course of a few months. In 6 of the 8 cases, *groups 2 (a)* and *2 (b)*, treated conservatively over long periods of time, exophthalmos was present on admission. One of the 2 patients in this group in whom the sign was not present on admission subsequently developed well defined exophthalmos during treatment and this persisted postoperatively. Suggestive prominence of the eyes developed in the other but rapidly disappeared.

Crile and Crile (8), in commenting on exophthalmos in children, stated their belief that early and adequate operation prevented in most cases the development of the symptom and advanced this finding as a reason for early operation. Marine (25) on the other hand presented some experimental evidence to show that exophthalmos might be the result of a gonad-thyroid-pituitary relationship and that exophthalmos might be closely related to thyroid insufficiency associated with an increased gonadal activity. The latter was thought to be mediated more particularly through the interstitial cells of the testis. He explained the lowered incidence of exophthalmos since 1922 reported by Plummer and Wilder (26) as perhaps due to the use of iodine in therapy with the consequently decreasing thyroid insufficiency in Graves' disease incident thereto.

Cardiac complications. Cardiac complications of importance are notably rare in children. The myocardial reserve is adequate to the strain which the disease puts upon the heart. Coronary disease has not appeared, and the bundle branches and valves are usually intact. Consequently abnormalities of rhythm and cardiac dilatation with decompensation are not usually observed. Dyspnea as a symptom was recorded in 7 of the cases. This was not the result of heart failure, however, and may be compared with the dyspnea experienced by normal individuals after a rapid walk up an incline or a game of tennis. No instances of cardiac arrhythmia were recorded.

Abnormal physical development. When the case records were reviewed with particular reference to any acceleration of growth which might have occurred in association with the onset of Graves' disease, no definite conclusions could be drawn for lack of data. In several instances, however, the histories recorded parents' statements to the effect that the child began to grow rapidly about the time hyperthyroid symptoms developed.

Dangers and Disadvantages of Thyroidectomy Performed Immediately the Patient Is Prepared

Avoidable surgery. That thyroidectomy as a procedure is avoidable in a small percentage of cases with juvenile Graves' disease is undoubtedly true. This is particularly true if cases of doubtful diagnosis are not rushed to operation without due consideration. Borderline, or doubtful cases are, however, not included in this discussion. Only those patients suffering severe and unquestioned Graves' disease are considered. As Lahey (27) has so aptly stated: "When there is doubt of the diagnosis of hyperthyroidism, that doubt should never be settled by operation, but by delay and by permitting the individual by his clinical appearance to prove the presence or absence of hyperthyroidism. There will be few cases in our experience in which this proof will not eventually demonstrate itself, one way or the other." If only undoubted cases are treated surgically, certain individuals will, nevertheless, be submitted to thyroidectomy whose symptoms might be satisfactorily arrested by conservative measures of therapy alone. Such a symptomatic "cure" was brilliantly illustrated in *case 12* of this series. As shown above, however, the evidence is preponderantly in the other direction; 83% of all cases conservatively treated subsequently required thyroidectomy. In the light of such a result with non-surgical treatment, one who prescribes this regimen must be quite optimistic to think that he can thereby eliminate any appreciable amount of surgery.

Postoperative myxedema. In reviewing the literature on juvenile Graves' disease, an impressive number of warnings about postoperative myxedema were found. There seems to be an almost universal fear that myxedema will develop in the child postoperatively and that this will subsequently seriously interfere with the child's normal growth and development. Consequently many surgeons advocate a conservative type of operation in which goodly portions of thyroid tissue are allowed to remain. This is also apparently a major objection to surgery expressed by those physicians who advocate a non-operative course of treatment.

In the group of cases reviewed in this series, the postoperative onset of 2 mild and transient cases of hypothyroidism was mentioned. In none of the cases was there any notation to indicate that growth and development was anything but entirely normal following operation. Girls whose menstrual periods had been abnormal or absent prior to operation had normal and regular menses, in most instances, within several months following thyroidectomy. Mental and physical development proceeded in an entirely normal manner except in the 2 cases of postoperative hypothyroidism and in those cases with persistent hyperthyroidism. The 2 patients developing hypothyroidism were, however, readily controlled with thyroid extract in small doses, and after a few months their thyroid glands functioned in a manner adequate to their needs. In reading the various reviews of case histories and case reports presented in condensed form earlier in this paper, one is impressed with the frequency of the warnings against radical operation, yet in no one of these papers is there mentioned one single instance in which a severe or permanent myxedema developed following operation. There is no record of any case in which postoperative development was found to differ from the normal. On the other hand, several writers (7, 10, 11) have taken the view that very radical thyroidectomies are safe in

children because of the ability of small amounts of thyroid tissue in the child to hypertrophy in a short time to such an extent as to make the gland adequate to all normal needs.

In summarizing the evidence on this point, the question arises as to whether the consistent omission of reported instances of severe and permanent postoperative myxedema in the several reviews of childhood Graves' disease was an oversight or whether significant hypothyroidism failed to develop. Furthermore, is it merely a strange coincidence that none of the present series of patients developed any serious hypothyroidism? It would seem reasonable that such is not the case and that the hazard of postoperative myxedema in serious degree has been made a mental stumbling block without justification.

Recurrence. Another argument which might be advanced against operative therapy as opposed to conservative treatment in children is that recurrences are said to be particularly prone to occur in the child. This marked tendency of the disease to recur in the adolescent has been noted and commented on frequently in the literature. In this series there were 3 postoperative recurrences (including cases of persistent hyperthyroidism), in the 16 cases undergoing operation, an incidence of 19%. These figures include one case operated on elsewhere and first seen in the New York Hospital with a recurrence. Gillette (28) writing on the subject of recurrent hyperthyroidism stated that after adequate thyroidectomy by capable surgeons recurrences in adults average 5 to 10%. He found that in most so-called recurrences the symptoms of hyperthyroidism had rarely regressed entirely after thyroidectomy. Welti (10) reported only 2 recurrences in his series of 24 cases. The 2 recurrences in his series were in the only patients on whom less radical operations were performed than usual. Greene and Mora (2) reported 4 recurrences in their group of 26 cases. Two of these cases responded satisfactorily to nonoperative treatment of their recurrences and the other 2 required a second operation. Proportionately less thyroid tissue was said to have been removed in this last series of cases than was usually excised in adults. In the present series the percentage amount of tissue removed at operation could not be determined as such estimates must necessarily vary from operator to operator. Without accurate information as to the percentage amounts of tissue operatively removed in a large series of cases together with a knowledge of their postoperative care, it is impossible to arrive at any worthwhile conclusion as to whether the exact extent of the amount of tissue removed constitutes a factor in the recurrence or persistence of symptoms in the child. This applies, of course, only to those cases in which subtotal thyroidectomies are performed.

It is of some interest that only 2 patients in the entire series failed to respond to iodine therapy preoperatively. One of these patients subsequently developed a recurrence of his Graves' disease and the other a mild postoperative myxedema. On the other hand, the most severe case in the entire group, *case 17*, on whom 3 subtotal thyroidectomies were performed before the disease became quiescent, had a prompt and satisfactory preoperative iodine response. It is also noteworthy that of the 2 recurrences with preoperative records both received preoperative iodine for periods less than 60 days and fall into *group 1* (q. v.) whereas no member of *group 2* (*b*) carried for a longer period on intermittent iodine therapy experienced a recurrence. All three of the recurrences in this series have come to a second thyroidectomy.

Whatever the answer to the problem of recurrence may be, and although it remains an outstanding hazard, the fact is that therapy other than operative has proved impracticable in this hospital. Arrest of the disease by conservative methods of therapy was not attained in a large enough percentage of the cases so treated to make these conservative methods desirable when unsupported by thyroidectomy. Moreover, the hazards accompanying such a conservative regime are so great that immediate surgery following adequate preparation becomes the procedure of choice and the procedure of necessity. The prognosis in those cases whose symptoms persist following operation or who experience recurrences is not good for reasons discussed elsewhere. On the other hand, if the problem is understood in its entirety and if in conjunction with appropriate medical and surgical therapeutic procedures a judicious and intensive program of psychotherapy is instituted as soon as the complication develops, the outlook need not be entirely gloomy.

SUMMARY AND CONCLUSIONS

An analysis prepared from the records of the New York Hospital of 18 cases of Graves' disease in children under 18 years of age is presented. Some of the pertinent recent literature is summarized and comparisons of the points of major interest made with the findings of the present study. The distinction between conservative, nonoperative management and early thyroidectomy following iodine preparation is especially emphasized and the results of these two therapeutic approaches contrasted and compared.

Preoperative and postoperative systolic and diastolic estimations of blood pressure, for the individual where available, and for the group, showed that in addition to the well-recognized systolic elevation associated with Graves' disease there was also a significant depression of the diastolic pressure. This diastolic depression amounted to 11.1% of the average postoperative diastolic pressure.

Routine blood studies showed no aberration in either the percentage or absolute numbers of lymphocytes in the peripheral blood or in the total leucocyte count in this series of patients with active Graves' disease.

Conservative, non-surgical methods of treatment failed to produce a permanent arrest of the disease in 5 of 6 patients (83%) in this series. Such measures also proved more costly and time-consuming than did programs of treatment entailing early thyroidectomy. The child's schooling was disrupted for longer intervals with conservative treatment. Moreover, in many instances home treatment mediated through the clinic proved impracticable because of lack of coöperation on the part of the patient.

Exophthalmos was present in 61% of the cases at the time of admission. Some degree of proptosis developed subsequently in an additional 33%.

Following thyroidectomy the growth and development of the operated children in the present series proceeded, in the absence of any recurrence, in an entirely normal manner. Postoperative myxedema of any permanent importance did not occur, and it would seem unlikely that such an eventuality need be seriously considered as contraindicating thyroidectomy. Postoperative recurrences and persistent hyperthyroidsm on the other hand occurred in 3 of the thyroidectomized cases. This complication apparently developed irrespective of the mode or duration of the preoperative or post-operative treatment and management. It would seem, therefore, that inasmuch as thyroidectomy has been shown to be a therapeutic necessity, the physician, while fully aware of the risk entailed, has no reasonable, alternative to advising such a procedure. In view of *a*), the inability of conservative, non-operative measures to arrest permanently the course of Graves' disease in children, *b*), the adverse effects of prolonged, non-surgical treatment, and *c*), the absence of demonstrable post-operative complications (except as discussed above), it is suggested that all children presenting the unequivocal syndrome of Graves' disease be subjected to subtotal thyroidectomy at the earliest moment compatible with adequate preparation therefor.

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Pancreatic Encephalopathy

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The occurrence of mental symptoms in organic pancreatic disease is at the present time but little discussed in standard works on diagnosis and psychiatry. Sadler (1) in his chapter on involutional melancholia quotes the work of Lovell (2) who observed fibrosis of the pancreas or focal pancreatic necrosis in patients afflicted with this psychosis. Lovell (3) published a series of observations in which anxiety as a psychotic symptom was associated with pathologic evidence of pancreatic disease. Pancreatic function tests applied to living patients showing this type of psychosis (4) showed no distinct results, for which, however, technical inadequacy of available laboratory tests used could well be claimed. Later, Drury and Farran-Ridge (5) added five additional observations on patients showing a similiar anxiety syndrome who died from pancreatitis. In their blood sugar studies on patients showing confusion and melancholia, curves demonstrating a disturbed sugar metabolism were frequent. Mann, too, found abnormal blood sugar curves in a large series of patients showing melancholia or anxiety neurosis. In his more recent discussion, Lovell (3) seems inclined to think that an alteration in the viscosity of the serum may precipitate the pancreatic lesions and cerebral edema which he considers the basis for the mental symptoms. Because of the fundamental importance of differentiating between individuals manifesting a psychosis without any demonstrable organic lesion and individuals in whom the psychosis is merely a symptom of an organic disease, we wish to add further observations on this interesting condition of psychosis occurring in association with organic pancreatic disease.

During the past four years, 8 cases have come under our observation which are thought to have characteristics sufficient to warrant their recognition as a distinct syndrome. We wish to report briefly their histories and autopsy findings and to discuss the mental symptoms, differential diagnosis, and the pathological lesions found at autopsy.

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Case Reports

Case 1. H. S., a 73-year-old female, was admitted Dec. 17, 1936, to the observation ward of St. Louis City Hospital, with the diagnosis of senile dementia. Six days prior to admission the patient had had a brief apoplectiform attack from which she seemed to recover. Three days later, she had a similar but more severe seizure, during which she was seen to hold her abdomen as if in great pain. In the next two days she had periods of semicoma and confused agitation, pacing the floor and refusing to eat or sleep. The physical examination revealed an elderly white woman in coma. The blood pressure was 140/80. The abdomen was bloated and tense but showed no definite rigidity. There was a waxy rigidity of the muscles of the extremities and extension was quite painful. The deep reflexes were hyperactive with bilateral ankle clonus. The laboratory data showed on admission a leukocytosis of 17,500, with 86% neutrophils. The urine contained albumin but no sugar; acetone was present. The spinal fluid was clear and under normal pressure. The Pandy reaction was positive; the cell count was 15. The blood diastase was 750 mg., the blood N.P.N. 36 mg. %. Serological tests for syphilis were negative. An x-ray of the chest showed an incipient pneumonia in the left lower lobe. With appropriate therapy the acidosis was cleared up and the patient returned to consciousness. It was then found that she was completely disoriented, confused and out of contact with the world. She was extremely irritable and would push away anyone trying to attend her. Her speech seemed slightly impaired and slurred. The blood diastase on the first day of hospitalization fell to 450, and reached normal levels on the following day, where it remained. The leukocytosis persisted for about 10 days, but the albumin in the urine cleared up within a short time after admission. The blood N.P.N. returned rapidly to the normal. The temperature, which at the onset of the disease ranged around 101° F., gradually subsided. After the 10th day in the hospital, the patient made rapid progress toward recovery. The speech

and the mental confusion cleared and the agitation subsided. On Jan. 10, 1937, she was discharged with the notation: "The patient shows no evidence of illness. She is rational, walks about, eats and sleeps well. She is fully oriented."

Case 2. A. T. R., a 70-year-old white female, was admitted to the Columbus State Hospital Aug. 13, 1938, in a confused and agitated state. She was resistive and talked incessantly and incoherently. The history obtained from the daughter gave the onset of the disease about one month prior to admission with complaints of abdominal distress, nausea and occasional vomiting. Shortly after this, the patient became quite restless and anxious, pacing the floor during the night and resisting any attempts of relatives to undress or bathe her. She developed an obstinate anorexia and even refused to take water. Physical examination revealed a moderately obese, acutely ill, elderly woman. The temperature was 103°F., the blood pressure 130/100. The abdomen showed slight tenderness in the epigastrium. The muscles of the extremities were definitely spastic with a waxy or cogwheel rigidity. The deep reflexes were hyperactive, the abdominal reflexes absent. There was no definite pathological toe sign. The laboratory data showed a total white blood count of 14,200. The urine contained 50 mg. % of albumin and a few granular casts. The van den Bergh reaction was positive. The N.P.N. of the blood was 34 mg. %. The spinal fluid was clear, under normal pressure, and contained only 16 cells. The liver function tests showed 36% retention of bromsulfalein after 30 minutes and an hippuric acid excretion equal to 2.32 gm. During her stay in the hospital her temperature gradually subsided and signs of pulmonary infiltration disappeared. There was improvement in speech and occasionally the patient made definite contact with her environment. She developed a marked grasping reflex, although she was quite resistive and tended to push people away from her. Decubital ulcers appeared over the sacrum and trochanters, and cellulitis rapidly extended over the whole right thigh. The patient developed hyperpyrexia and died on her 28th day in the hospital.

The autopsy showed an atherosclerosis of the mitral valve, sclerosis of the coronary arteries and aorta. The liver presented the picture of fatty degeneration. The uterus was the site of multiple fibroids and an endometrial polyp. There were extensive decubital ulcers present with a spreading cellulitis of the right thigh. The pancreas was small and showed a definite decrease in the amount of glandular tissue but without gross scarring or inflammation. Scattered throughout the peripancreatic fat many pinhead flecks of whitish material were seen. There was no evidence of old or recent hemorrhage. Histologically small focal areas of fat necrosis could be found surrounded by slight inflammation. Periductal fibrosis was present with duct dilatation and obstruction of the lumen. In some areas a diffuse infiltration of the pancreatic tissue with round cells was noted. Histological examination of the remaining organs showed vascular necrosis with small hemorrhages in the brain, small hemorrhages into the myocardium, severe fatty degeneration of the liver with no evidence of bile duct disease, and chronic inflammation of the mucosa of the bladder.

Case 3. A. R., a 60-year-old white female, was admitted to the Columbus State Hospital Sept. 15, 1939, in an agitated and confused state. Her husband revealed that the patient had had 'stomach trouble' off and on for a number of years. She also had had numerous attacks of depression but not sufficiently severe to require institutionalization. The present attack began 48 hours before admission when she complained of some abdominal distress. She vomited several times, refused to eat, became restless and agitated and rapidly slipped into a depressed condition. Her speech was very slow and gradually became mumbling and disconnected, until finally there was complete incoherence. The muscular movements were slow, her gait unsteady. Physical examination revealed an acutely ill, elderly woman having a temperature of 103.8°F. Her lungs showed bronchial vesicular breathing with loud râles over both sides. The blood pressure was 180/90. The abdomen showed some tenderness in the epigastrium but no rigidity. The muscles of the extremities and neck were spastic with 'waxy' rigidity. Extension of the muscles produced pain. The deep tendon reflexes were hyperactive but equal. The abdominal reflexes were absent. The laboratory data revealed a leukocytosis of 10,100 with 81% neutrophilic leukocytes. The urine contained a few hyaline casts. Six days after admission the blood diastase was 70, the urine diastase 1900. The serological reaction was negative for syphilis. Her temperature gradually subsided and her lungs cleared up entirely. On admission the patient had been very restless and confused, refusing to stay in bed and sleeping poorly, but she regained some measure of orientation and awareness of her surroundings. However, the severe nausea persisted and even small feedings produced vomiting. In a short time the patient developed a profuse diarrhea of semiliquid, light brown, foul smelling stools. The urinary diastase decreased to normal levels (440), but rose again to 870. Temperature elevation set in concurrently with the diarrhea. The patient received parenteral fluids and repeated blood transfusions without checking the diarrhea. She grew acidotic, developed hyperpyrexia, and died on the 23rd day in the hospital.

The autopsy revealed an old rheumatic valvular heart disease, a generalized arteriosclerosis with nephrosclerosis, an extensive ulcerative colitis, and an acute hemorrhagic cystitis. The pancreas was grossly normal in size and shape and did not show any evidence of hemorrhage or fat necrosis. No permission for autopsy of the brain was granted. The microscopic examination of the pancreas showed numerous microscopic areas of glandular necrosis, severe periductal fibrosis with epithelial hyperplasia and metaplasia. Numerous small areas of fat necrosis could be observed with or without inflammatory reaction. The microscopic examination of the ulcers of the colon showed a severe necrotizing process suggesting bacillary dysentery. Bile duct fibrosis and slight fatty metamorphosis were observed in the liver. Some bilt ducts were markedly dilated, the epithelium hyperplastic.

Case 4. J. B., a 65-year-old white female, was first admitted to the Columbus State Hospital in January 1929. At that time she stated that she had been troubled for a long time by 'gastritis' and 'bad liver.' For the past

two years this abdominal trouble had been gradually getting worse with a steady loss of weight. Six months previous to admission she was in an automobile accident, which was a great shock to her, and two months after the accident she developed psychotic changes with delusions of persecution and hallucinations. She had been eating fairly well during this time but had suffered a great deal of indigestion. The physical examination at this time revealed a systolic blood pressure of 185, generalized sclerosis of her arteries, an absence of abdominal reflexes and a diminution of the deep tendon reflexes. Her mental status showed numerous persecutory delusions and hallucinations which kept the patient restless during the night. The speech was free, rambling, and disconnected. The patient gradually recovered from her delusions. In July 1929, she was discharged with the note, "She is in very good condition mentally. She has complete insight into her condition and remembers very well all the hallucinations and delusions she once had." In September 1934, the patient was readmitted by voluntary commitment. In the past 3 months she had had a gradual return of her nervousness and in the past week had developed delusions of persecution and hallucinations. The physical examination was essentially the same as on the previous admission. The mental examination showed good orientation and excellent insight. She appeared mildly depressed. The hallucinations and delusions of the patient, which kept her extremely noisy and restless, gradually cleared up and she was discharged in October 1935. She was readmitted to this institution for a third time in October 1935, again by voluntary commitment. She stated that she got along very comfortably most of the time but occasionally had a bad time with her stomach, which at times gave rise to vomiting and great distress in the region of the gallbladder. Her physical examination was essentially the same as on previous admissions. Mentally she was perfectly oriented and her memory was little impaired for both recent and remote events. During the succeeding 4 years, the patient had recurring intervals of mental clarity and apparent rationality alternating with periods of acute hallucinations and delusions with great agitation and restlessness. The psychotic episodes were often accompanied or preceded by attacks of gastric distress with nausea and vomiting. In January 1939, she developed abdominal distention, nausea, protracted vomiting and elevation of temperature. She died 36 hours later.

The autopsy revealed advanced sclerosis of the coronaries, an acute volvulus with gangrene of the intestines, and surgical absence of her appendix and female sex organs. The pancreas weighed only 75 gm. It showed innumerable whitish-yellow spots in and around the glandular tissue, giving the typical speckled appearance of extensive fat necrosis. No permission for the examination of the head was granted. The microscopic examination showed diffuse extensive fat necrosis of the pancreas with massive inflammatory reaction. The pancreatic ducts showed fibrosis with dilatation and epithelial hyperplasia. The interstitial fibrous tissue was not markedly increased. There was a moderate fibrosis of the bile ducts without signs of recent obstruction or inflammation. The liver showed severe chronic passive congestion with central degeneration of the liver lobules. The kidney showed moderately advanced nephrosclerosis.

Case 5. K. S., a white female, was first admitted to the Columbus State Hospital in July 1932, at the age of 59. She voluntarily applied for commitment and was diagnosed psychoneurosis, neurosthenic type. The patient stated that 7 years ago she developed a persistent pain of varying intensity in the right upper quadrant, for which she consulted a dozen or more physicians. Finally she was operated upon and a 'shriveled' gallbladder containing one large stone was removed. Only a little relief was obtained from this operation, and many other physicians were consulted. At the time of admission, she had innumerable complaints, among which were pain beginning at the upper right quadrant of the abdomen and radiating downward into the thighs, nausea, excessive gas on the stomach, occasional severe epigastric pains, and constipation alternating with frequent attacks of diarrhea. Physical examination revealed a well nourished white woman, apparently not acutely ill. The blood pressure was 122/68. The abdomen showed some tenderness to deep pressure in the epigastrium but no rigidity. The deep tendon reflexes were normal, and no ankle clonus and pathologic toe sign could be elicited. Mentally she was well oriented in all spheres; the memory was unimpaired, the general information and knowledge good, the judgment fair, her insight questionable. She was quite irritable, complaining and critical. She was discharged in October 1932, as improved. She was readmitted in April 1935, with similar complaints and was said to be extremely hypochondriacal. Physical examination revealed essentially the same findings as on the previous admission. During the next two years she made frequent trial visits to her home, and the clinical notes revealed nothing but the usual references to her neurosthenia and hypochondriasis. She was discharged in September 1937, as improved. The patient was admitted for the third time in October 1937, again complaining as before. Physical examination was unchanged. In November 1939, she began showing some ataxia and a diminution of mental clarity. Her speech became incoherent and she obstinately refused to take nourishment of any kind. She gradually became weaker, developed râles in the bases of both lungs and considerable dyspnea. Her temperature elevated to 105°F., and she died shortly after.

The autopsy showed myocardial fibrosis, lobar pneumonia, generalized arteriosclerosis with special involvement of the renal and coronary vessels. The pancreas was small, weighing only 40 gm. The glandular substance was markedly decreased and replaced in good part by fat tissue. The organ showed numerous adhesions and considerable gross scarring. Numerous small whitish and yellow pinhead sized spots were scattered throughout the organ. The brain weighed 1,100 gm. The precentral area on the left side was shrunken and the sulci appeared widened. The ventricles were not dilated. Sectioning of the brain revealed no gross pathological changes. The basal arteries showed only moderate sclerosis. The microscopic examination of the pancreas showed considerable periductal fibrosis with epithelial metaplasia. The interstitial fibrous tissue was markedly increased. The glandular tissue as well as the interlobular fat tissue showed

patchy infiltration with inflammatory cells. Numerous areas of fat necrosis and of glandular necrosis were present, surrounded by an intense inflammatory reaction. Other necrotic areas appeared calcified and encapsulated. Numerous depositions of free or intercellular hemosiderin gave evidence of previous hemorrhages. Sections through the brain showed a generalized hyperemia. In some areas small perivascular hemorrhages were noted. In other sections perivascular areas of myelin degeneration and edema were present with occasional scavenger cells filled with lipoid material. The ganglion cells in those areas appeared swollen and loaded with lipoid granules. The lipoid substance was indistinct and the oligodendroglia appeared increased. The meningeal vessels showed no remarkable pathological changes.

Case 6. J. H. M., a 60-year-old white male, was admitted to the University Hospital Jan. 13, 1939, complaining of severe abdominal pain. The patient had left home the same morning to take his daughter to school. He remembered stopping his car near the school, but the remainder of the day was a complete blank to him. He was found by the police wandering through the streets at midnight, in a disoriented state. For the past year his family had noticed a gradual change in his personality and he "seemed to turn against his own family." Some recent financial difficulties had occurred, and the patient had been requested to make good a shortage of funds entrusted to him. The physical examination showed a well developed and well nourished white male, complaining of severe abdominal pain. The skin and sclerae had an icteric tint. The base of the left lung showed dullness to percussion. Auscultation over this area showed evidence of bronchial breathing with numerous moist râles. Marked rigidity of the upper abdomen, almost boardlike in character, was present. Palpation produced severe pain which was specifically pronounced over the epigastrium and the left upper quadrant of the abdomen. The white blood count showed a leukocytosis of 23,150, with 95% polymorphonuclear leukocytes. The urine contained 10 mg.% of albumin. The patient's course was rapidly downhill. He became semicomatose, cyanotic, and his temperature rose to 104.2°F. The patient expired the next day.

The autopsy showed a moderate generalized arteriosclerosis. The pancreas and the surrounding fatty tissue showed extensive hemorrhagic necrosis with partial liquefaction. All vessels in this area, including the splenic artery, showed recent thrombosis. The liver and gallbladder showed no pathological changes. The brain weighed 1,450 gm., and the cut surface showed a few areas suspicious of hemorrhage. The microscopic examination of the pancreas revealed the typical picture of acute hemorrhagic pancreatitis with diffuse and severe inflammatory reaction in the periglandular tissue. The areas of necrosis were very large and showed extensive hemorrhages. In the non-necrotic parts of the pancreatic tissue, little evidence of a previous disease of the organ could be noted. The ducts appeared normal, and the lumina and the interstitial fibrous tissue were not narrowed. Microscopic examination of the various sections of the brain showed distinct capillary necrosis with perivascular edema and hemorrhage. Most of the extravasated blood cells were hemolyzed. The larger vessels did not show any arteriosclerosis, nor were there present any degenerative lesions of the nerve tissue. Section of the liver showed no evidence of bile duct disease.

Case 7. J. S., a white male, age 53 years, was admitted to the Columbus State Hospital on July 8, 1933, with symptoms of fear, depression, and confusion. He showed great anxiety to the degree of mild violence, and his stream of talk was disconnected, voluble, and at times entirely irrelevant. He had no insight, although his general information was good. No hallucinations or delusions were elicited. Physical examination showed a well developed, well nourished adult male. His blood pressure was 180/120. His speech was slightly tremulous and his fingers showed some tremors. The deep tendon reflexes were normal. The white blood count was 14,900 with 83% neutrophils. The urine analysis was not remarkable. The serology report revealed nothing abnormal. About 6 years after admission, he had a fainting spell, after which he became decompensated, but with appropriate therapy was able to be up and about again. In the 6 months preceding death, he had three distinct and severe heart attacks. He also complained of some cramps in his abdomen. In February 1940, he developed an irregular pulse and dependent edema. One month later he died suddenly.

The autopsy showed a coronary thrombosis with extensive myocardial infarction. Infarcts were found in the lungs and spleen. The gallbladder showed evidence of chronic inflammatory changes. The pancreas appeared grossly normal. The brain showed a small cystic area suggestive of an old encephalomalacia in the region of the left internal capsule. There was severe sclerosis of the brain vessels. Microscopic examination of the pancreas showed small areas of glandular and fatty necrosis with a weak inflammatory reaction. There was slight interstitial fibrosis and proliferation of the epithelium of the larger ducts. The brain sections showed small petechial hemorrhages with necrosis of the vessel wall and hemolysis of extravasated blood. There was also evidence of considerable cortical atrophy with sclerotic changes of the ganglia cells, increase in amyloid bodies, and replacement gliosis. The larger vessels showed a moderate degree of arteriosclerosis.

Case 8. A. LeM., a 55-year-old white female, was admitted to the Columbus State Hospital on July 12, 1940, in a semicomatose condition from which she could be aroused with difficulty. It was revealed that she had been a known severe case of hypertension for several years and had complained frequently of stomach disorder. In 1925, she had developed an addiction to morphine, from which she was definitely cured. In the last year she began to drink alcoholic beverages and became a rather heavy imbiber. Four weeks before admission her gastric distress became so acute that the patient could take nothing but bread and milk. During this period the patient developed confusion, agitation, insomnia and visual and auditory hallucinations. Her speech became slurred and incoherent. Physical examination showed a well nourished female with a blood pressure of 260/165. There was pitting edema of the lower extremities and the face appeared bloated. The heart sounds were accentuated and there

was a definite tenderness in the epigastrium. The extremities showed waxy, cogwheel rigidity. The tendon reflexes were hyperactive, the abdominal reflexes absent. The ankle clonus was poorly sustained, toe sign indeterminate. The laboratory findings showed mild anemia with moderate leukocytosis. The urine contained considerable albumin, white cells, and a few red cells. The B.U.N. was 20 mg.%, the blood cholesterol 246 mg.%. The blood diastase determined by the Somogyi method was 241 mg. The urine diastase showed a reduction of 30,000 cc. of 0.1% starch solution by a 24-hour specimen. The patient was given nicotinic acid in daily doses of 1,000 mg. and 50 mg. thiamin chloride intramuscularly. Within three days she showed a definite clearing of the sensorium. The patient talked fairly well and seemed better oriented. The edema receded and the pulse became full and forceful. Respirations, however, remained poor and the patient was rather feeble. A week after admission the patient lapsed into a Cheyne-Stokes type of respiration, being comatose during the apneic phase and lucid during the hyperpneic. She finally sank into coma from which she could not be aroused and died.

The autopsy findings showed an extensive hemorrhage of the cerebellum, excavating much of the left and a portion of the right hemisphere. Extensive subarachnoid hemorrhage covered the posterior and inferior surfaces of the cerebellum. The brain was rather soft but revealed no remarkable pathology. The pons and medulla oblongata showed no hemorrhage. There was a chronic peptic ulcer in the stomach and evidence of chronic pelvic inflammatory disease. The kidneys showed moderate nephrosclerosis and pyelitis. The pancreas was smaller than normal, weighing about 85 gm. On section numerous pinpoint, whitish spots could be noted, suggesting glandular necrosis. The periglandular fat was normal. The microscopic examination of the pancreas showed a diffuse interstitial fibrosis with marked vascular sclerosis and moderate duct fibrosis. Some proliferation of the ductal epithelium with metaplasia was observed. The glandular tissue appeared atrophic in the fibrous areas. Some small capillaries appeared necrotic; others were plugged with hyaline thrombi. Numerous small hemorrhages were present which elicited a weak cellular reaction. In other sections small areas of fat necrosis were found surrounded by an inflammatory reaction. The walls of the small arteries contained calcium bodies. Sections through the brain revealed evidence of advanced arteriosclerosis with extensive deposits of corpora amylacea. Areas of gliosis and recent encephalomalacia were present. The meningeal vessels showed marked thickening of the intima. The brain vessels showed in some sections perivascular pigment deposits suggestive of old hemorrhage. The cerebellum was the site of profuse hemorrhage. Sections through the kidney showed an advanced pyelonephritis with strumification of the cortex and moderate nephrosclerosis.

CLINICAL DISCUSSION

The description of mental symptoms in pancreatic disease has been largely confined to the state of hyperinsulinism and diabetes mellitus, where their occurrence is now quite generally acknowledged (6). While we feel certain that the cases presented in the foregoing do not even remotely fall into either of these two categories, nevertheless, the question arises as to whether we are dealing with a definite syndrome which is sufficiently characteristic to permit the clinical diagnosis. From the psychiatric point of view, the syndrome is characterized by many atypical features. In every one of our cases the staff diagnosis which was eventually made was admittedly uncertain and not unanimous. The cases were usually recorded as senile psychosis or cerebral arteriosclerosis. One was designated as a typical manic-depressive psychosis and another was given the generic appellation of "psychosis with other somatic disease." The psychotic picture presented resembled in many respects that of an acute toxic psychosis. The onset was usually rather abrupt with confusion and marked agitation. Vivid auditory and visual hallucinations developed in some cases, and delusions of persecution appeared. There was a marked speech defect of a slurring type which when understood was found to be incoherent and irrelevant. There was often complete disorientation and total lack of insight and judgment. At the onset the agitation resembled acute anxiety and depression as emphasized by Lovell (3) but often this disappeared after a time and the patient became irritable, resistive and belligerent. We often noted the expression in the eyes, which suggested awareness and mental clarity. Lucid intervals appeared during which the patient conversed fairly rationally and intelligently. However, these were usually of short duration.

The neurological examination revealed certain features which seemed to us characteristic and which we do not find emphasized in the literature. There was usually a pronounced spasticity of the muscles of the extremities and sometimes of the neck. The muscular rigidity was that of a 'waxy' or 'cogwheel' type, and it was noted that extension of any muscle group gave rise to pain. The deep tendon reflexes were usually hyperactive but equal. The abdominal reflexes were absent in all our cases, and ankle clonus or a pathologic toe sign was noted occasionally. In the later stages of the disease a strong grasping reflex manifested itself, which seemed to annoy the patient no little in view of his resistive and uncoöperative tendencies. The cranial nerve tests did not yield any unusual results, and the ocular fundi of the patients so examined were not remarkable.

The progress of the disease showed a strong tendency to spontaneous recoveries and relapses. The agitation and confusion subsided gradually and the hallucinations disappeared. The patient then regained his orientation and showed a surprising recovery of

his memory. Although many of our cases fell in the age group in which senile or arteriosclerotic psychoses are common, we have rarely observed psychoses of this type showing such marked agitation, confusion and disorientation to recover so completely all mental faculties. The first case had complete clinical recovery within one month of the onset. Two cases showed repeated attacks with complete recovery in the intervals. Unless the lesion in the pancreas was very severe, as in *case 6*, the condition proved non-fatal per se and death was due to some other apparently unrelated cause.

Very interesting with regard to the etiology of the psychotic manifestations was the past history of the patients as elicited from the relatives at the time of admission. In all our cases except one, recurrent attacks of gastric distress, or 'stomach trouble,' had been present either for many years before any mental changes were noted or had occurred just shortly before the onset of the psychosis. As a rule the patient's relatives failed to mention these symptoms because of their great concern over the recent psychotic manifestations, but persistent questioning in this regard revealed a very definite story of pains in the abdomen, loss of appetite, nausea and vomiting. Furthermore, there was often an obstinate refusal on the part of the patient to take anything by mouth, even water. Some of our patients entered the hospital with severe dehydration and acute somatic illness in addition to their psychosis. In *case 6*, the abdominal distress was so great that it pointed distinctly to the correct diagnosis. In the other cases the physical examination at the time of admission gave only a few clues to any abdominal disorder, consisting in some residual tenseness in the epigastrium and tenderness on pressure.

It is now generally recognized that pancreatic disturbances are associated with an enormous rise in the blood diastase, and this test is being applied universally in cases of undiagnosed abdominal distress. The unfortunate disadvantage of this test is that the diastase remains elevated in the blood for a very short time only. The urinary diastase determination while admitting greater ranges of error, is more practical in that its elevation is slower and may not subside for a few days after the blood has returned to normal levels. In the first case the patient was brought into the hospital on the third day of her acute illness and the blood diastase was found to be markedly elevated. In the third case the blood diastase was normal six days after admission, but the urinary diastase was significantly high. In the last case both the blood and urinary diastase were elevated. The second case showed a definite evidence of disturbed liver function and bile duct disease similar to that reported by Salzman (7). Those patients who were examined during the onset of the acute attack showed a marked leukocytosis with increase in polymorphonuclear leukocytes as evidence of an acute inflammatory process within the body.

In summary, we believe that this syndrome illustrated in our case reports bears sufficient characteristic features from the psychiatric as well as the neurologic point of view to lend itself to the proper differential diagnosis. The evidence of actual organic brain lesions concomitant with the psychotic manifestations and the comparatively good prognosis as far as recovery was concerned seemed to us sufficiently typical to suspect the clinical diagnosis. This suspicion could be partially verified by review of the somatic history of the patients, the physical examination, and the performance of suitable laboratory tests. At autopsy further evidence was obtained as to the character of the brain lesions in patients suffering from pancreatic disease, which is discussed in the following section.

PATHOLOGY

In the 7 cases which died under our observation, permission for postmortem examination was obtained. In only 5 cases could a complete autopsy, including examination of the brain be performed. Five of the patients who came to autopsy were women, two were men. They all had died between 53 and 77 years of age. Three of them were moderately obese, while 5 showed clinical and anatomical evidence of long-standing hypertension. None of the bodies showed any characteristic constitutional stigmata. The peritoneal cavities of 6 of our cases showed marked adhesions in the upper right abdominal quadrant in the region of the gallbladder, the duodenum and the head of the pancreas. In three cases postoperative adhesions were found in the pelvis or appendiceal region. In 4 cases the liver was much smaller than normal and weighed only a little over 1,000 gm. Microscopical evidence of some degree of chronic cholangitis with periductal fibrosis and round cell infiltration was observed in three cases. Three livers showed a moderate fatty metamorphosis. In 1 case the gallbladder gave evidence of chronic inflammatory disease with a stone present. *Case 6* died of a widespread acute hemorrhagic pancreatitis. *Case 8* died of an extensive cerebellar hemorrhage. The causes of death in the other 5 cases were: diffuse cellulitis of the leg: acute ulcerative colitis; volvulus with gangrene of the intestine; confluent bronchopneumonia and coronary thrombosis.

The pancreas was carefully studied in all 7 patients. It was normal in weight and there were no gross pathological changes in three instances. In 4 cases it was definitely reduced in size, weighing between 40 and 75 gm. The glandular tissue was de-

creased in amount and the fibrous tissue was increased. There were numerous adhesions between the pancreas, the duodenum and the stomach. On close examination the organs of all 4 cases showed numerous whitish-yellow spots of pinhead size and varying consistency in and around the glandular substance. It gave the organs of *cases 2, 4, 5,* and *8* a speckled appearance. The pancreas of *case 6* showed all the characteristic changes of an acute and severe hemorrhagic pancreatitis. Microscopically, pathologically significant lesions could be found in every one of our cases, including those which appeared normal grossly. They were sufficiently numerous to be apparent in any of the sections examined and are illustrated in figures 1 to 8. They consisted principally in more or less sharply circumscribed areas of fatty or glandular necrosis, some of them calcified and partly encapsulated, others apparently recent in origin and associated with an acute inflammatory reaction. *Case 6* revealed microscopically a typical acute hemorrhagic pancreatitis with a diffuse violent reaction in the interstitial and mesenteric tissue. *Case 4* also showed a rather diffuse inflammatory reaction in the pancreas with confluent areas of necrosis without hemorrhage. In 6 cases definite microscopic evidence of chronic inflammatory conditions could be demonstrated in the gland. The principal lesion was a marked periductal fibrosis with dilatations of the medium-sized and smaller ducts and epithelial proliferations with metaplasia. Severe interstitial fibrosis leading to atrophy of the glandular tissue was present in three cases. Small foci of round cell infiltration were numerous, and deposits of hemosiderin pigment in some of the fibrosed parts suggested previous hemorrhages. Vascular sclerosis to any remarkable degree was present in only two cases. *Case 6*, which showed severe acute inflammatory changes, did not give any evidence of previous organic disease. *Case 7* showed the characteristic changes of advanced pancreatic cirrhosis with diffuse interacinar changes as described by Whipple (8). Three of the more obese patients showed fat infiltration between the fibrosed lobules as well as inside the lobules.

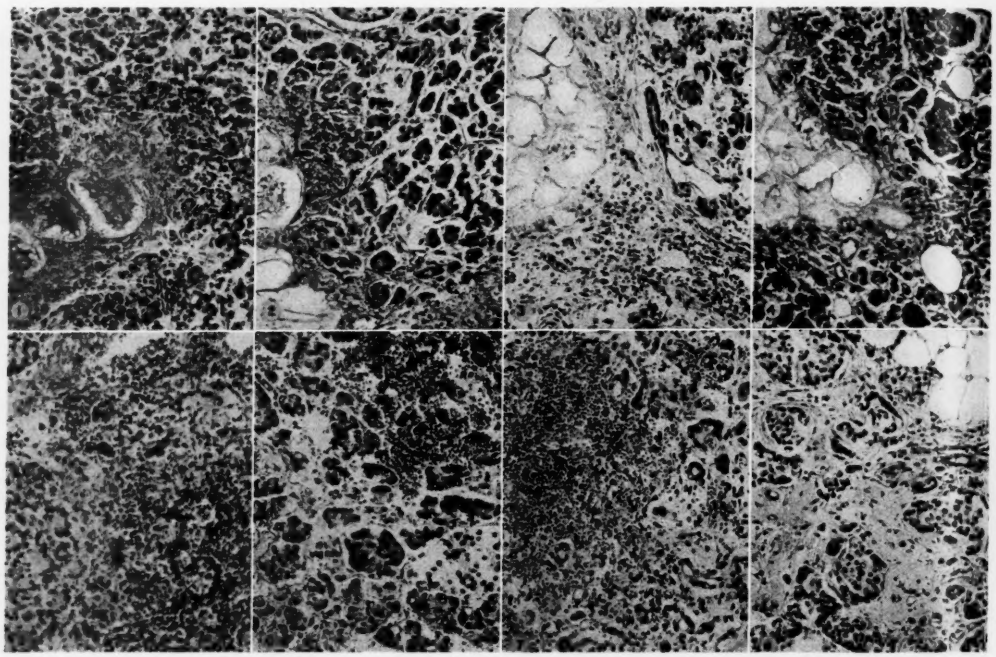

Fig. 1–8. SECTIONS OF PANCREAS of *cases 2* to *8*, showing different degrees of glandular and fat necrosis accompanied by hemorrhage, acute and chronic interstitial pancreatitis. 1, *Case 2*. 2, *Case 3*. 3, *Case 4*. 4, *Case 5*. 5, *Case 6*. 6, *Case 7*. 7, 8, *Case 8*.

The brain was examined in 5 cases only. In two patients it was normal in weight and revealed no gross pathological changes. In one case (*case 5*) it was decreased in size. The sulci were widened, the meninges thickened. In *case 7*, a similar cortical atrophy was noted and a small brownish cystic area was found in the region of the left internal capsule measuring 5

mm. in diameter and suggesting a previous vascular accident. The brain of *case 8* was the site of a severe cerebellar hemorrhage. Microscopic examination of selected tissue blocks from various parts of the brains showed the following details (fig. 9–14). Cortical atrophy with ganglion cell changes typical of advanced cerebral arteriosclerosis was present in 2 cases. In both instances numerous corpora amylacea cases consisted of small focal areas of capillary hemorrhage associated with perivascular edema and reactive gliosis. These petechial hemorrhages were especially numerous in the patient who died of acute pancreatitis. In the other cases sometimes several sections had to be studied before evidence of petechial hemorrhages was found. They were located most frequently in the central ganglia or close to the lining of

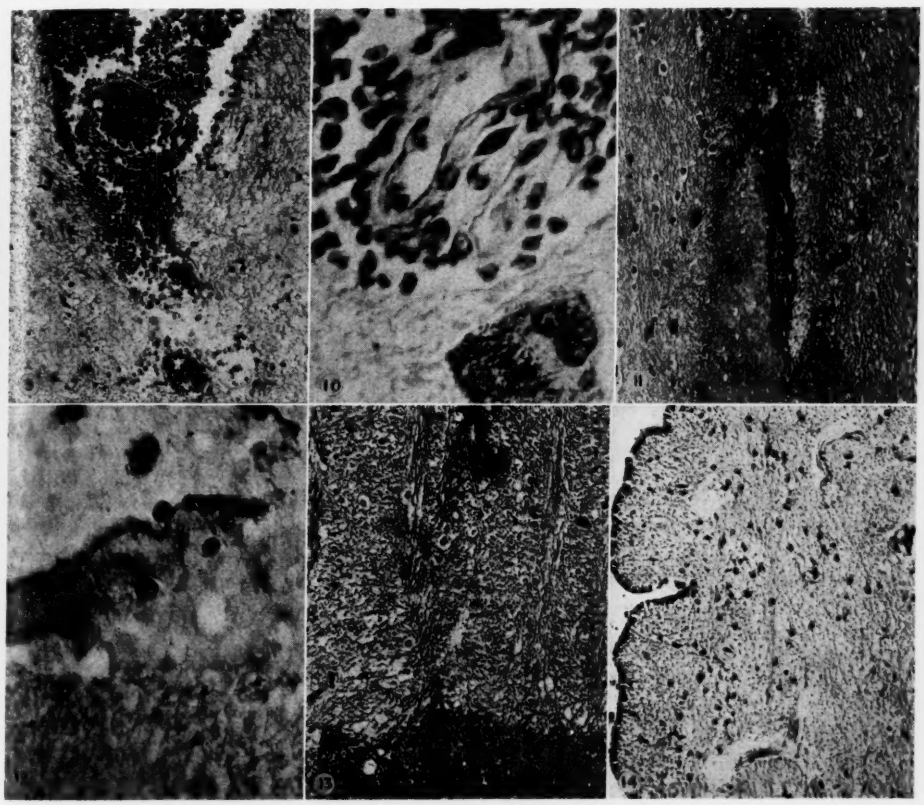

Fig. 9–14. Sections of brain of *cases 2, 5, 6, 7,* and *8,* showing capillary necrosis with hemorrhage and edema, lipoidal granulation of ganglia cells and subependymal gliosis. 9, *Case 2.* 10, *Case 5.* 11, *Case 6.* 12, *Case 7.* 13, 14, *Case 8.*

were found beneath the ependymal lining of the ventricles, and sections through the central nuclei showed porencephalic changes. In one case there was severe vascular sclerosis with marked thickening of the walls of the meningeal vessels and narrowing of the lumina. It was this case which died from acute cerebellar hemorrhage. Small multiple areas of old or more recent encephalomalacia were present throughout the white substance. In 3 cases the cortex as well as the brain vessels showed no senile or sclerotic changes. The lesions which were present in all 5 the ventricles. They were present only occasionally in the cortex and in the white brain substance. The amount of extravasated blood was never very large and in some instances merely filled the dilated Virchow-Robin's spaces. Occasionally it seemed to compress the lumen of the capillary. Some of the petechiae were quite recent with excellent preservation of the red blood cells; in others decomposition of hemoglobin with pigment formation was already in progress. While in many instances no pathology of the bleeding capillary could be noted, a definite necrosis

with hyalinization of the vessel wall was evident in other sections. Sometimes the lumen of the bleeding vessel appeared to be occluded by a homogenized or hyalinized blood clot. These petechial hemorrhages were found regardless of the senile or sclerotic vascular changes present. Some of the vessels were surrounded by an increased number of glial cells, while others showed merely hemosiderin pigment as evidence of previous hemorrhages. In no instance could we find the severe encephalitic picture as described by Salzman, although many of the areas of perivascular gliosis may have deserved a similar interpretation. Subependymal gliosis and ependymitis were present in 4 cases. We did not observe an increase of the vascular bed in the central nuclei of the brain as described by Bender and Schilder (9) in their group of alcoholic psychoses.

An interpretation of the neuropathological findings and their correlation with the lesions of the pancreas can naturally at this point be only speculative. The existence of a transient acute pancreatitis in humans is now clinically well recognized (10), and considered by some a not uncommon occurrence (11), and is quite frequently associated with diseases of the biliary tract (12). Spontaneous recovery is the rule and there is never need for operative interference. These clinical observations agree well with Whipple's pathological studies, who found small areas of pancreatic or fat necrosis, not a rare observation at the autopsy table. In 230 routinely studied pancreatic glands of 300 consecutive autopsies, 41 cases of focal necrosis, 5 cases of fat necrosis, and 7 cases of circumscribed hemorrhagic pancreatitis were found. Focal necrosis had occurred in many acute intoxications such as pneumonia, septicemia, peritonitis and typhoid fever. He considers their occurrence as an important etiological factor in the development of chronic diffuse pancreatitis. Our own statistical studies of this problem seem to agree with Whipple, although our incidence has not reached such high figures. Distant lesions in other organs during acute pancreatitis have been described and include the recent observations of Leidler (13) (vestibular apparatus), Irbach (14) (skin disease), Roux and Girault (15) (hemorrhagic rectal colitis), Úsua Mariné (16) (muscular hematoma), and Dittler and McGavack (auricular fibrillation (17). Far reaching effects of pancreatic enzymes, whose increase in the blood represents a highly important step in the clinical diagnosis, could well be considered as etiological factors in the light of the experimental work of Necheles and Neuwelt (18), Friedman and Katz (19). Powell (20) explained the occurrence of mental symptoms in pancreatic dyscrasias as the result of "cerebral malnutrition," while Lovell (3) considered a change in the surface tension of the blood serum as basis for psychoses in pancreatitis. He felt that this change gave rise to cerebral edema and varying degrees of encephalitis.

Another etiological relationship may be speculated upon on the basis of the work by Bender and Schilder and Jolliffe, et al. (21). In 1930, Bender and Schilder presented a group of psychoses to which they applied the generic term "encephalopathia alcoholica." Under this they distinguished 5 different groups of symptoms dependent upon the most prominent manifestation but felt that fundamentally they all had the same etiological basis. The apparent similarity between their group of "clouding of consciousness and changing rigidities" and our own cases necessitates a more critical comparison. In both instances slurring speech, changing rigidities of the extremities accompanied by athetoid movements and a strong grasping reflex were present. Clouding of consciousness of various depths and delirious features and hallucinations were also observed. Differing from Bender's group, the deep tendon reflexes were always hyperactive in our cases, and a strong tendency to spontaneous recovery was noted. Furthermore, in only one of our cases was there any history of excessive alcoholic consumption. The microscopic lesions of the brain again showed a striking likeness, which we have emphasized in a foregoing paragraph. Bender and Schilder thought that alcohol and other toxic products had to be considered as the causative factors of the neuropathological lesions, although Wechsler (22) in his discussion reiterated the belief that the lesions were caused by an associated vitamin deficiency. Jolliffe and his group have reported recently that even far advanced cases of so-called alcoholic encephalitis could be cured in many instances by appropriate therapy with nicotinic acid and felt that the disease was essentially a vitamin deficiency which should be labelled "nicotinic acid deficiency encephalopathy." It could easily be possible that the pancreatic disease through its consequent frequent gastric upsets and disturbances of appetite precipitated a similar vitamin deficiency in our patients. Such lack of proper nourishment over a period of time may well be sufficient to produce the acute nicotinic acid deficiency as described by Jolliffe. This mechanism seems to offer a more satisfactory explanation than the attempt to associate the psychosis directly with concomitant enzymatic alteration of the blood. Taking cognizance of this fact, we administered to one patient (*case 8*) large doses of nicotinic acid and produced a remarkable improvement of her symptoms within a short time. Should further therapeutic trials with this vitamin bear out the correctness of our assumption, the syndrome described in our eight cases would be correctly classified as a type of nicotinic acid deficiency encephalopathy (Jolliffe) precipitated by organic pancreatic disease.

Finally, it should be added here that we believe this syndrome of pancreatitis and encephalopathy to be more common than one might at first consider from this paper. By our own restrictions we have limited the cases reported herein only to those with positive evidence (laboratory or autopsy) of acute pancreatitis. This meant the elimination of quite a number of patients in whom the diagnosis could be made only clinically, that is, in patients who were seen too late in the disease for the blood and urinary diastase to be elevated and whose recovery precluded autopsy examination.

SUMMARY

1. A series of eight cases are described which showed a fairly typical neurological syndrome characterized by anxiety and agitation, clouding of consciousness, muscular rigidities and speech disturbances. The neuropathological lesions consisted primarily in capillary necrosis and petechial hemorrhages with perivascular and subependymal gliosis.

2. The history, physical examination and clinical laboratory tests revealed that all eight patients suffered from more or less severe organic pancreatic disease. This was substantiated by the autopsy findings where circumscribed or diffuse areas of glandular or fat tissue necrosis could be observed together with evidence of chronic interstitial pancreatitis.

3. On the basis of comparative clinical and pathological considerations, it is believed the condition described herein and illustrated with eight case reports is a specific syndrome of acute pancreatitis and encephalopathy. The suggestion is made that the pancreatic disease precipitates acute nicotinic acid deficiency which in turn is the true etiologic factor of the neurologic and psychotic manifestations of the encephalopathy.

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Creatine-Creatinine Metabolism in Older Patients with Benign Prostatic Enlargement[1]

[Androgens and Prostatic Enlargement]

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THE DISTURBED RELATIONSHIPS of androgens and estrogens has from time to time been suggested as an important factor in the etiology of benign prostatic enlargement. To date, no convincing evidence has appeared to support this hypothesis. In the present report, the creatine retention test has been utilized as a possible measure of the effective androgen level in man.

Benign prostatic enlargement occurs more frequently after middle age, usually between 55 and 65 years of age and in these years of life sexual potency may diminish, even to the degree of complete impotence. This experience led many workers to conclude that since benign enlargement and loss of sex power occurred at about the same time, they were both due to the same cause, mainly a change in testicular or androgenic function, or to a change in balance of estrogens and androgens.

Many workers advocate the hypothesis that there is a decrease of male sex hormone in benign prostatic enlargement. Kochakian (1) found that men 50 to 76 years of age excreted only about one-sixth of the amount of androgen excreted by young men between 22 to 29 years of age. Rusch and Kundert (2) were able to conclude only that there was a significant decrease from normal, and Dingemanse, Borchardt and Laqueur (3) were able to demonstrate only a slight variation which, even in the so-called normals, overlapped the lower levels of androgenic excretion in the older men. However, Vest and Howard (4) could find no essential difference in comb-growth response between androgens excreted by young normal males, 20 to 26 and 32 to 40 years of age and by older men, 64 to 82 years of age, with and without benign prostatic enlargement. Moore et al. (5) have shown that there is less excretion of urinary androgens in old men, with and without benign prostatic enlargement, than in young men. There is much variation in the older men neither of the groups showing a sharp difference in the excretion of urinary androgens, as expressed in international units.

Moore and McLellan (6) after using adequate doses of testosterone propionate over long periods of time, could find no significant restoration of the involuted prostate of presenility, nor observable alteration of the histologic appearance of the tissues formed in benign prostatic hypertrophy. Others (7) working on the same principle of the administration of androgens in an already pathological enlargement of the prostate, and making a biopsy at the first stage of a suprapubic operation, were unable to show any change. Nor is there pathologic or histologic evidence (8), that the action produced by castration or any hormone influences the course of prostatic hypertrophy.

It was shown by the comb-growth method of urinary androgen assay (9) that a high degree of urinary excretion of testis hormone in men in the prostatic age group "is not necessarily associated with the presence of a prostatic adenomatous growth." Further, that "findings do not tend to lend support to the theory that adenomatous enlargement of the prostate gland is caused by hyper-testis endocrine activity."

Adequate proof for this theory of androgenic imbalance has not as yet been presented.

The standards of previous work are based upon the amounts of androgenic hormone excreted in the urine or detected in the body tissues or circulating blood. Although various levels are constantly found in these sources, they do not necessarily represent the actual amount of hormone utilized in the body by

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active endocrine metabolism. To date these theories are supported only by the assay of the excretion products of the body which are obviously waste or non-utilizable substances in the process of being cast off. A method which tests the retention of exogenous creatine more nearly meets the requirements of proof, although it, too, is an indirect method.

It has been shown that children of both sexes have a spontaneous creatinuria (10) and can retain only a portion of exogenous creatine, generally having a poor creatine tolerance up to 13 years of age (11, 12, 13). After puberty, creatinuria does not occur in the normal male, but does occur in some normal women (14, 15, 16). Also, men generally retain exogenous creatine better than do women (11, 17, 18, 19).

Buhler (20) later demonstrated that creatinuria could be reduced by androgens in cases of so-called sexual hypofunction and that in old men and women with endocrine dysfunction the response is similar to that of children. Remen (21) had previously shown impairment of creatine retention in old age (71–90 years) and after castration. These workers conclude that the male gonad has a regulatory influence on creatine metabolism. Read (22), in a study of 5 Chinese eunuchs, showed a constant creatinuria in prepuberal castrates.

Shrire and Zwarenstein (23) found no creatine in the urine of castrated adult male rabbits, but recently, Coffman and Koch (24) demonstrated that in rats castrated when 3 months of age, creatine retention following exogenous creatine can be increased and the intense creatinuria decreased by means of testosterone propionate therapy. This work was substantiated by Kenyon et al. (25, 26) who used 4 eunuchs and a eunuchoid and were able to show that daily administration of 25 mg. of testosterone propionate caused a marked increase in the creatine retention following the daily ingestion of creatine.

Creatinuria can be produced by causes other than gonadal dysfunction or hormonal imbalance. Many observers (16, 27–31) have reported the constant presence of creatinuria in such pathological conditions as acute fevers, wasting types of chronic diseases, tumor cachexia, exophthalmic goiter, acute and chronic infectious diseases, diseases entailing starvation and acidosis, primary and secondary muscular dystrophies, as well as in infants and children, starving adults, in castrates and eunuchoids, in some normal women after menstruation, during pregnancy and after parturition, and during menopause.

The recent works of Pizzolato and Beard (32) present unusual findings concerning creatine and creatinine metabolism in that they claim to induce creatinuria in both male and female rats after castration by administering testosterone, estrogen, anterior pituitary extracts, cortin, saline, and water.

The excretion of creatinine is also said to be affected by the hormones. Shrire (33) and his coworkers noted that after a latent period of 3 months following castration and ovariectomy in the rabbit there is an increased creatinine excretion. This phenomenon was also observed by Kun and Peczenik (34). Lasch (35) in his studies of 20 elderly men (60–82 years of age) noted in many of them that the endogenous urinary creatinine values were lower than in earlier years. Kenyon et al. (25, 26) were unable to find any change in the creatinine excretion in eunuchs, eunuchoids, or normal men and women after the administration of testosterone propionate.

Jailer (36) recently completed a careful study of the effect of castration and androgen therapy on creatine-creatinine excretion in monkeys. He did not note any significant increase in creatinine values after castration in monkeys. He also cited a case of a human castrate observed for 9 months after castration, with no treatment, and in which no significant increase in urinary creatinine occurred. He further showed that a spontaneous creatinuria and an impaired retention of exogenous creatine usually occurs in young male monkeys. After testosterone propionate therapy, the creatinuria is abolished and the capacity to retain exogenous creatine is increased. In mature monkeys there may or may not be a creatinuria, but the capacity to retain exogenous creatine is marked. After castration in mature monkeys there is increased creatinuria and impaired creatine retention which, if the animal is treated with testosterone propionate shows a restoration of capacity to retain creatine and a disappearance of the creatinuria. Thus, it is readily demonstrated that by removal of the testes of a mature male monkey it is possible to produce a condition similar to that in an immature male monkey as directly related to the creatine-creatinine metabolism. Furthermore, this similarity in metabolism in the immature and castrated male monkey may be altered by injecting each group with testosterone propionate causing the metabolism of creatine and creatinine to resemble that in the normal mature male monkey which is known to be able to retain exogenous creatine. So it would seem that the ability of these animals to retain exogenous creatine depends, for the most part, upon the presence of androgenic substances secreted by the testis, and that this capacity for retention is found only in the mature animal after the assumption of the physiological action of an internal secretion of the testis. Jailer's work in monkeys shows the same results as those which many previously mentioned workers have reported in the human; that is, that the presence of this male hormone in sufficient and supposedly normal amounts in the human adult male will result in an ability to retain on an average of

not less than 70 per cent of administered exogenous creatine.

There has been much speculation concerning the increase or decrease of androgenic hormone in man in relation to age, and the possible relation of the imbalance to benign prostatic enlargement. This report is an attempt to estimate the relationship through the medium of creatine-creatinine metabolism expressed in terms of the creatine retention test as compared to normal (70%). This figure should not be below that of a so-called normal value if there is an increase of androgen excretion in elderly males.

METHODS AND MATERIALS

The patients used in these tests were normal young males, elderly males who exhibited no clinical signs or symptoms of benign prostatic enlargement, and elderly patients whose clinical signs and symptoms of benign prostatic enlargement demanded surgical intervention.

Twenty-four-hour-urine specimens were collected and chemically analyzed for their content of creatinine according to the method of Folin (10), and creatine according to Jailer's modification of the method of Benedict and Myers (37).

It was necessary to select patients who showed no evidence of eunuchoidism, hyperthyroidism, infectious diseases, cachexia and chronic wasting conditions, muscular dystrophies, and other conditions in which a spontaneous creatinuria occurs. Although in cases of eunuchoidism, the creatine excretion is usually only 10 to 30% of the creatinine values, in the other conditions there may be as much as 50 to 100 per cent excretion of creatine. Diabetics were excluded from these groups of patients because it is known that glucose and acetone bodies interfere with the Jaffe reaction. However, in one case not reported here, a diabetic controlled by means of insulin and diet showed no variation from that of the average elderly male with benign prostatic enlargement. Obviously patients with any suspected evidence of carcinoma were not used.

In all, approximately 62 patients were examined and determinations of creatinine and creatine in the urine were made. Since many of the results were discarded because of technical errors suspected in complete 24-hour-urine specimens, lack of cooperation, or the unexpected dismissal of patients from the hospital, this report represents data on only 42 patients of those examined.

Generally the routine consisted of a physical examination, including rectal, routine urine examination, tests for the retention of urine, blood count, non-protein nitrogen in the 'non-prostatic' and blood urea nitrogen and creatinine in the 'prostatic' group and cystoscopy in the cases of patients presenting signs or symptoms of benign prostatic enlargement.

The patients were placed on a meat-free diet (milk if desired) at the beginning of the experimental period. The 24-hour-urine specimens were then collected and determinations made for creatinine and creatine excretion. In all except the normal young male patients a short series of determinations were made to standardize the average daily output of creatinine and creatine before giving the creatine retention test. The creatine retention test consists of giving the patient 2 grams of creatine hydrate by mouth (equivalent to approximately 1.76 gm. of creatine) and determining the urinary creatine during the following 24 hours.

The following groups of patients were studied:

a) '*Prostatic*' (*12 patients*).

Since there is a relative loss of renal function in all patients suffering from a chronic obstruction at the outlet of the bladder, it was necessary to make 4 to 5 creatinine standardizing determinations on these patients preoperatively. Three to 4 were made postoperatively before giving the creatine retention test (C. R. T.).

The determinations were made after urethral drainage was established by an indwelling catheter, both preoperatively and postoperatively, in order to avoid an undue loss of urine. The postoperative determinations were made sufficiently long after suprapubic prostatectomy (19–28 days, and in one case 61 days) to obviate any of the effect of surgical procedures upon the creatine excretion.

b) *Elderly* '*Non-prostatic*' (*11 patients*).

Selected from Columbia-Presbyterian Eye Institute. Determinations were made either before or after cataract operations.

These patients showed no evidence of prostatic enlargement or any other involvement of the genito-urinary tract, and the non-protein nitrogen of the blood was within normal limits. Aside from the eye condition, the only changes from normal exhibited by these elderly males were those that might be expected due to advancing years.

Three standardizing tests were done before giving the creatine retention test.

c) '*Prostatic*' (*6 patients*). *Before and after testosterone therapy.*

These were selected from the prostatic *group a*, listed above, several months after hospital discharge.

Without the standardizing determinations, the creatine retention test was given. The patients were then injected with testosterone propionate[3] intramuscularly, receiving 200 mg. in divided doses over a two-week period. The creatine retention test was

[3] Perandren, Ciba Pharmaceutical Products, Inc., Summit, N. J.

then repeated on the complete 24-hour-urine specimen.

d) *Normal Young Males (6 patients). Before and after testosterone therapy.*

These individuals were tested and treated in a similar manner to the prostatic patients in *group c* above. They showed no evidence of any involvement of the genito-urinary tract.

RESULTS

There was as much a variation in the results of the creatine retention test in each individual as there was between the various individuals concerned in the selective groups. In the prostatic patients, *group a*, whose average age was 59.8 years, there was a marked individual variation of the excretion of the creatinine. The age and weight coefficients in these cases may be disregarded, since we are dealing with patients suffering from renal imbalance subsequent to obstruction by the prostate at the bladder neck. There was an average creatinine nitrogen coefficient of 5.7 for this group, whereas the normal coefficient for adults is 7.5 to 11.7. These were true values, because the urines were collected by means of an indwelling catheter with presumably no loss of urine.

In the preoperative group of tests the prostatic patients showed no constant increase or decrease in excretion of preformed creatinine after the ingestion of exogenous creatine; 7 of the patients showed a decrease while in 5 there was an increase. In the same group postoperatively, 8 excreted less, and 4 patients showed an increase in creatinine excreted.

The main interest in this problem was the ability of the patient to retain exogenous creatine. In the prostatic group, preoperatively, the average creatine retention was 82.3% (table 1). The highest retention was 100.0% while the lowest was 55.9%. Except for this latter, which was the only extremely low figure, the rest of the creatine retention values were above 70.0%, the majority of them being 83.6% and up. The average postoperative creatine retention was 80.9%. This shows an average difference of 1.4% in the preoperative and post-operative tests which is not significant. The lowest postoperative creatine retention test was 62.7, while the highest was 91.7%, and here also the majority retained upwards of 82.6%. The average of the preoperative and postoperative creatine retention tests in the elderly prostatic group was 81.6%.

TABLE 1. CREATINE-CREATININE BALANCE IN ELDERLY PROSTATICS

Case	Age	Preoperative					Postoperative[3]				
		Control Period[1]		Exogenous Creatine[2]		C.R.T.	Control Period		Exogenous Creatine		C.R.T.[4]
		Preformed Creatinine	Total Creatinine	Preformed Creatinine	Total Creatinine		Preformed Creatinine	Total Creatinine	Preformed Creatinine	Total Creatinine	
		mg.	mg.	mg.	mg.	%	mg.	mg.	mg.	mg.	%
1	52	1292	1371	1276	1338	96.5	686	725	664	1319	62.7
2	52	964	1015	924	1452	70.0	1446	1476	1696	1884	89.3
3	53	1872	1881	1948	2138	89.2	1353	1458	1650	1796	91.7
4	54	944	1000	1151	1667	70.6	804	833	705	1101	77.5
5	55	1420	1428	1215	1323	93.9	1438	1474	1318	1883	67.9
6	59	817	867	800	1326	70.1	682	752	610	822	87.9
7	61	1578	1594	1742	2033	83.6	1264	1254	1107	1271	90.7
8	63	642	672	908	1683	55.9	880	886	838	1138	82.6
9	66	501	525	176	282	94.0	1033	1076	893	1250	79.9
10	67	697	731	774	988	87.8	767	789	928	1203	84.4
11	67	777	777	532	532	100.0	685	725	616	865	85.8
12	68	1024	1037	756	1176	76.1	1079	1067	1130	1657	70.1
Av.	59.8					82.3					80.9

[1] Control period = average of preliminary estimations to standardize excretion of creatinine and endogenous creatine.
[2] Represents single creatine retention test.
[3] Creatine retention test performed 19 to 61 days postoperatively.
[4] C.R.T. (creatine retention test) = % of exogenous creatine retained in the first 24 hours after ingestion.

The controls for the prostatic group consisted of elderly non-prostatic patients, *group b* (table 2), whose average age was 63.3 years. The creatine retention in this group average 78.9%, or only 2.7% less than the combined averages of the group of prostatics. The creatinine nitrogen coefficients were lower than in healthy young males; they are within normal limits. The coefficient averaged 6.4 in this instance, while it was only 5.7 in the case of the prostatics, but in the former there were no evidences of a renal insufficiency. In this group of non-prostatics the lowest per cent of creatine retention was 59.6, while the highest was 95.1%.

In the comparison of the two groups (tables 1, 2)

TABLE 2. CREATININE AND CREATINE EXCRETION AND CREATINE RETENTION TESTS IN ELDERLY NON-PROSTATICS

Case	Age	Control Period[1]		Exogenous Creatine[2]		C.R.T.[3]
		Preformed Creatinine	Total Creatinine	Preformed Creatinine	Total Creatinine	
		mg.	mg.	mg.	mg.	%
1	54	1040	1119	1149	1859	59.6
2	56	1290	1397	1418	1958	69.3
3	57	1123	1201	1201	1448	85.9
4	58	973	1014	1089	1564	73.0
5	62	1044	1069	1040	1535	71.8
6	62	1281	1307	1280	1921	63.5
7	63	844	851	955	1047	94.8
8	66	1222	1316	1305	1542	86.5
9	69	1312	1388	1148	1338	89.5
10	72	1072	1089	1069	1445	79.2
11	77	1057	1100	1037	1123	95.1
Av.	63.3					78.9

[1] Control period=average of preliminary estimations to standardize excretion of creatinine and exogenous creatine.
[2] Represents single creatine retention test.
[3] C.R.T. (creatine retention test)=% of exogenous creatine retained in the first 24 hours after ingestion.

the prostatics averaged 3.5 years younger, and retained an average of 2.7% more of exogenous creatine than the non-prostatics. These differences are without significance.

No standardizing tests were done on the normal young males before the creatine retention tests were given. The average retention was 79.3%, which increased to only 80.9%, or 1.6% more, after administering the testosterone propionate therapy. The average of the creatinine nitrogen coefficient in this group was found to be 9.1, or well within the normal range of 7.5 to 11.7. One patient, *case* 3, was excluded from the general averages because of his unexplained atypical reaction, involving a fall in the creatine retention from 84.4 to 56.8% after treatment with testosterone propionate (table 3).

TABLE 3. CREATINE RETENTION TESTS BEFORE AND AFTER ANDROGEN THERAPY IN NORMAL YOUNG MEN

Case	Age	Control[1]			200 mg. Testosterone Propionate during 2 Weeks in Divided Doses		
		Preformed Creatinine	Total Creatinine	C.R.T.	Preformed Creatinine	Total Creatinine	C.R.T.
		mg.	mg.	%	mg.	mg.	%
1	24	1560	1888	81.3	1568	1881	82.2
2	24	1953	2308	79.8	1835	2254	76.2
3[2]	30	1550	1824	84.4	831	1601	56.8
4	31	1472	1728	86.0	1423	1882	73.9
5	34	1201	1342	92.0	1129	1193	96.3
6	37	2457	3202	57.6	2485	2912	75.7
Av.	30.0			79.3			80.9

[1] Control period=creatine retention test before testosterone propionate therapy.
[2] *Patient* 3 not included in general average due to unexplained atypical reaction.

Six prostatics were selected at random from the group listed in table 1 and were given testosterone propionate. This group (table 4) with an average age of 60.3 years, showed an average creatine retention of 75.8% as compared with 81.1% which was the group average of creatine retention, preoperatively and postoperatively, of the same patients (table 1). Here also there is a variation of values of the same individual, at different times.

After testosterone propionate therapy the creatine retention increased to 85.0%, which was 9.2% more than that of the pretreatment values. Since there is a 10% technical error this increase is not significant.

Neither normal young males nor elderly prostatics displayed a marked increase in the percentage of creatine retention after testosterone propionate therapy (tables 3, 4).

TABLE 4. CREATINE RETENTION TESTS BEFORE AND AFTER ANDROGEN THERAPY IN ELDERLY PROSTATICS[1]

Case	Age	Control[2]			200 mg. Testosterone Propionate during 2 Weeks in Divided Doses		
		Preformed Creatinine	Total Creatinine	C.R.T.	Preformed Creatinine	Total Creatinine	C.R.T.
		mg.	mg.	%	mg.	mg.	%
1	52	1349	2210	51.0	1521	1960	75.0
2	55	1431	1763	81.5	1559	1695	92.3
3	59	882	928	98.0	1041	1155	93.5
4	63	1188	1850	62.3	1315	1788	73.1
5	66	1206	1476	84.6	1244	1653	76.7
6	67	1007	1403	77.5	955	963	99.5
Av.	60.3			75.8[3]			85.0[3]

[1] Patients in whom the creatine retention test was repeated several months after prostatectomy.
[2] Control period=creatine retention test before testosterone propionate therapy.
[3] Average of preoperative and postoperative C.R.T. in this group was 81.1%.

The three group averages of the creatine retention tests of prostatics (table 1), non-prostatics (table 2), and normal young males (table 3) may be compared.

The normal young males (average age of 30 years), elderly non-prostatics (average age of 63.3 years), and the elderly prostatics (average age of 59.8 years) had respective percentages of creatine retention of 79.3, 78.9 and 81.6%, after the ingestion of exogenous creatine.

This demonstrates the ability of the different age groups in the adult male to retain exogenous creatine in similar proportions.

DISCUSSION

The results of these experiments are striking. The creatinine nitrogen coefficient appeared to be generally lower in the elderly patients, both prostatics (5.7) and non-prostatics (6.4), than in the normal young males (9.1). The difference of 2.7 between young males and elderly non-prostatics is probably due to general decreased cell metabolism seen in elderly inactive individuals as compared to the activity and vigor of the young.

After the administration of exogenous creatine in prostatics, the excreted creatine in milligrams were found to form only 23.6% (preoperative) and 24.9% (postoperative) of the total creatinine. The average of the two would be 24.3% as compared with the average of 24.3% in the elderly non-prostatics, and 17.4% in the normal young males. After testosterone propionate therapy in the young males this percentage decreased to 6.7, indicating an increased retention. Four of the 5 patients showed a lessened average output in milligrams of total creatinine from 2094 to 2024 which represents only an amount of 3.3%, which is not significant. In this group of prostatics selected at random, it was found after administration of exogenous creatine that the average excretion in milligrams of creatine represented only 26.7% of the totalcreatinine values. After testosterone propionate therapy, this figure fell to 18%, while 4 of 6 patients showed a lessened average output of only 3.3%. In 4 of the 6 cases of young males the preformed creatinine decreased after testosterone propionate therapy to an average of only 2.3%, which is unimportant.

The patients of these three groups show no significant difference in their capacity to retain exogenous creatine. Young men, who presumably had normal androgen production, were given testosterone propionate but this treatment did not significantly increase their capacity to retain administered creatine.

The two groups of elderly patients showed about the same capacity to retain creatine as the younger age groups. Administration of testosterone to certain of the elderly patients failed to increase their capacity to retain exogenous creatine, which would occur if an androgen deficiency existed.

The use of the creatine retention test, with administration of androgen or without such medication, is suggested as a measure of androgenic function. In the observations reported here there is no marked difference between the three groups of patients in their capacity to retain creatine. This offers the suggestion that the physiological effectiveness of the androgens, at least in metabolic actions, of these older men is not significantly different from that of the young control group.

CONCLUSIONS AND SUMMARY

Many workers conclude that there is an increase or a decrease of androgenic hormones which results in a hormone imbalance causing benign prostatic enlargement. The results of this experiment, lead to a different conclusion.

Normal young males, after the administration of exogenous creatine show a creatine retention above an average of 70%. Elderly non-prostatic individuals after the administration of exogenous creatine show a creatine retention comparable to that of normal young males. Elderly prostatic patients, after the administration of exogenous creatine show a creatine retention comparable to that of normal young males and elderly non-prostatic individuals.

The creatinine nitrogen coefficient is generally lower in old age than it is in youth. The creatinine nitrogen coefficient is lowered in cases of obstructive uropathy.

There was no indication of a constant increase or decrease in creatinine values after testosterone propionate administration in young males or elderly males.

It would appear that creatine retention, as seen after the administration of exogenous creatine, is largely dependent on the androgenic substances formed by the physiological action of the adult testes, and that the loss of this action results in a markedly impaired creatine retention.

Inasmuch as it is found that the creatine retention in prostatic and elderly non-prostatic persons is parallel to that of the normal young male, it must be assumed that each of the three above-mentioned groups utilize the same amounts of androgenic hormone in their body tissues, this would seem to be evidence that in old age there is no marked increase or decrease of androgenic substances, at least up to and beyond the prostatic age.

A comparison of age groups in this experiment does not indicate a disturbance of the androgenic balance in patients with benign prostatic enlargement, although many workers attribute the enlargement to an increase or decrease of androgenic substance.

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Biologic Assay of Blood Estrogens by the Intravaginal Application of Extracts and Desiccated Material[1]

[Blood Estrogens]

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SINCE FRANK AND HIS COWORKERS (1) in 1925 demonstrated the presence of estrogenic substances in the circulating blood of women, many investigators have studied this problem. In most instances the procedures employed have consisted of various methods of extracting the hormones from the blood and conducting the bio-assays on spayed rodents by the Allen-Doisy technic. Frank and Goldberger (2, 3, 4) used alcohol and ether for extraction, Neumann and Peter (5) ether, Freed (6) acetone and ether, and Mühlbock (7) benzene. In each of these methods a relatively large amount of blood (20 to 50 cc.) was required and only a limited number of test animals could be injected for each analysis. Fluhmann (8, 9, 10) sought to avoid this objection by using untreated blood serum for direct injection into spayed mice and noting sub-threshold histologic changes in the vaginal mucosa, but this method involved killing the animals at the conclusion of each test as well as the preparation of microscopic slides.

The present report concerns a test for estrogenic hormones which requires only a small amount of blood, eliminates elaborate chemical extraction and the necessity for histologic preparations, and in addition allows the repeated use of the test animals.

Sensitivity of Rats to Intravaginal Application of Estrogens

A fundamental principle which has arisen from recent endocrine studies is that local effects of hormones may be greatly enhanced by applying them directly to responsive tissues instead of relying on the usual methods of hypodermic administration. This observation is well illustrated by the work of Berger (11) and Stadler and Lyons (12), who showed that cornification of the vagina of spayed animals can be produced with much smaller dosages of estrogens applied directly to the mucosa than can be effected by parenteral administration.

Since the test reported in this paper is based on this assumption, the work of the above named authors was repeated with a series of spayed rats.

As in all of the experiments of this study, the animals were ovariectomized rats of the Stanford strain, approximately 2 to 4 months of age. At various times when they were not in actual use they were primed with the subcutaneous injection of 30 to 50 I.U. of estrone. In addition, small amounts of estrone dissolved in sesame oil were periodically applied to the vagina as a test for the maintenance of sensitivity.

Four groups of animals received varying amounts of an estrone preparation made from a sample of the International Standard according to the technic described by Rowlands and Callow (13). From this original mixture solutions were prepared so that 0.02 cc. of sesame oil contained 0.05, 0.10, 0.15 and 0.20 I.U. respectively. On 2 successive days 0.01 cc. was carefully introduced into the vagina of the animals by means of a Breed and Brew micropipette. In doing this, great care was exercised that the outside of the pipette did not carry oil which inadvertently could be deposited in the vagina. The control animals received plain sesame oil administered in the same manner. Vaginal smears were examined 52, 60 and 72 hours after the first application. The reaction was considered positive whenever cornification was induced and even if nucleated epithelial cells and a few leucocytes were present.

It is seen from table 1 that negative results were obtained in 72 controls which received plain sesame oil. On the other hand, cornification resulted in 18% of the rats given 0.05 I.U. of the estrone preparation,

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in 58% receiving 0.1 I.U., 66% with 0.15 I.U., and 91% with 0.2 I.U. These figures attest to the sensitivity of this procedure and corroborate the observations of Stadler and Lyons (12). As a further check on the animals which gave positive results, they were injected intravaginally with sesame oil 5 days after the completion of the experiment and cornification did not appear in any case.

TABLE 1. INTRAVAGINAL APPLICATION OF OIL SOLUTIONS OF INTERNATIONAL STANDARD OF ESTRONE

No. of Animals	No. of I.U. Injected	% Positive Reactions
16	0.05	18
12	0.10	58
15	0.15	66
12	0.20	91
72	sesame oil	0

On the basis of these findings it may be said that 1 biologic R.U., as determined by this modification of the Allen-Doisy test, is equivalent to 0.1 U of the International Standard of estrone.

Assay of Blood Extracts

In earlier studies an acetone-ether extract of whole blood was employed for bio-assay by intravaginal application (14). Lyons and Templeton (15) and Yerby (16) previously had reported analyses of the estrogen content of urine conducted in a similar manner. From 10 to 15 cc. of non-citrated whole blood was mixed with 5 volumes of acetone and shaken for 10 minutes. The supernatant fluid was removed by filtration and the precipitate shaken twice for 5 minutes with three volumes of acetone. The acetone solutions were combined and dried by evaporation. This residue was extracted with ethyl-ether to which was added a small amount of sesame oil. The ether was then evaporated and the oil made up so that each 0.02 cc. contained the estrogen extracted from 0.5 to 2.0 cc. of the original blood volume. The assay was conducted as described previously with groups of 3 rats receiving extracts of various strengths. A single intravaginal application of 0.01 cc. was made daily for two successive days and smears were studied in 52, 60 and 72 hours. The response was considered positive when 2 of the 3 rats in each group showed a smear of cornified cells.

The results obtained by this means with 31 specimens of blood from patients with various gynecologic disturbances are shown in table 2. In every instance estrogen was demonstrated in amounts varying from 50 to 300 units of estrogen per 100 cc. of blood. In a rough way this may be held as representing an activity equal to that of from 5 to 30 I.U. of estrone.

Desiccated Blood and Pellets

In an attempt to improve this method of assay and to eliminate chemical extraction, it was found that much greater amounts of the hormone can be demonstrated by using pellets made from desiccated blood. The blood was measured and placed in a cellophane tube suspended in front of an electric fan at room temperature (17). In a few hours it was completely dried and after 10% of sesame oil had been added to the resultant powder it was hammered into small pellets weighing from 40 to 80 mg. in a machine such as has been described by several authors for making pellets of crystalline hormone material (18, 19). In some cases the blood was centrifugalized and separate analyses made of the serum and cells as well as of whole blood.

TABLE 2. ACETONE-ETHER EXTRACTION OF WHOLE BLOOD FOR ESTROGENIC HORMONES

Patient	Clinical Diagnosis	Day of Cycle	R.U. per 100 cc. Whole Blood
AB	Dysmenorrhea	10	200
		17	300
		24	200
		6	>100
AC	Dysmenorrhea	8	50
		15	<150
		23	> 50
		1	> 50
AD	Sterility	26	> 50
		7	200
		14	150
AE	Sterility	28	> 50
AF	Sterility	23	>100
		10	> 50
		20	<100
AG	Menorrhagia	35?	< 70
		?	> 50
AH	Menorrhagia	18	< 50
		18	> 50
AI	Menorrhagia	27	> 50
		9	< 20
AJ	Menorrhagia	25	> 50
		31 ?	> 50
AK	Climacteric		50
AL	Climacteric		> 50
AM	Amenorrhea		> 50
			> 50
AN	Amenorrhea		> 50
			> 50
			100
			> 50
AO	Amenorrhea		100

The pellets were inserted into the vagina of spayed rats by first placing them in thin glass tubes. The glass tubes were introduced into the vagina, the pellets held with a trocar and the tubes then carefully withdrawn. The pellets generally were completely dissolved in 24 hours, and vaginal smears were made in 52 and 62 hours. The same criteria were used for estimating the biologic results as with the oil solutions, and since 1 cc. of whole blood, serum, or cells dried by this procedure weighs on an average of 212, 110, and 300 mg. respectively, the amount of fresh material represented by each pellet was easily calculated.

In order to determine if the pellets could induce cornification of the spayed rat vagina merely by irritation, a series was prepared using blood from a woman who had been surgically castrated and who had been estrogen-free on previous examinations. These pellets weighed from 40 to 60 mg. and were inserted in the vaginae of a control group of 20 spayed rats. In no instance did cornification occur, so that it may be assumed that this histologic change is not produced merely by the presence of this type of foreign body.

The results obtained by this method are given in tables 3 and 4. Table 3 lists the findings of a group where the blood was assayed both after extraction with acetone and ethyl-ether and with pellets. It is seen that 2 to 4 times more units of estrogenic hormone per 100 cc. of blood were demonstrated with pellets than when chemical extraction was employed.

TABLE 3. ESTROGEN CONTENT OF WHOLE BLOOD AS DETERMINED AFTER CHEMICAL EXTRACTION AND THE USE OF PELLETS

Patient	Clinical Diagnosis	Day of Cycle	R.U. per 100 cc. Blood	
			Acetone-ether extraction	Pellets
BA	Dysmenorrhea	20	> 50	350
		2	> 50	300
		9	100	400
		16	>100	450
BB	Dysmenorrhea	11	<200	560
		21	100	380
		1	<100	350
BC	Dysmenorrhea	12	100	350
		16	>100	340
		23	150	320
BD	Sterility	13	100	370
		21	>100	>300
		28	100	300
BE	Polymenorrhea	22	100	400
		11	>100	>300
BF	Polymenorrhea	18	100	350
		25	>100	300
BG	Amenorrhea		100	350
BH	Amenorrhea		100	450
BI	Climacteric		>100	350
			>100	450
BJ	Climacteric		> 50	>300

TABLE 4. ESTROGENIC HORMONE CONTENT OF WHOLE BLOOD AS DETERMINED BY THE INTRAVAGINAL APPLICATION OF PELLETS

Patient	Diagnosis	Day of Cycle	R.U. per 100 cc.
CA	Amenorrhea		300
			<300
CB	Amenorrhea		260
			<300
			<300
CC	Amenorrhea		300
			<300
			<300
			<300
CD	Menorrhagia		520
			350
CE	Menorrhagia	25	350
CF	Metrorrhagia	15	370
		18	350
			300
CG	Metrorrhagia	15	>400
			<300
CH	Polymenorrhea		350
CI	Sterility	13	370
		21	<300
		28	300
CJ	Climacteric		450
CK	Climacteric		<260
CL	Climacteric		350
CM	Climacteric		>300
CN	Amenorrhea		420

DISCUSSION

Although the employment of blood pellets applied intravaginally as described in this report demands somewhat delicate technical manipulation, the results support the contention that this method is a very sensitive test for the quantitative determination of estrogens in the blood. The amounts of the hormone found in the patients of this series appear to be higher than those estimated in studies conducted by other means. The number of specimens obtained at regular intervals from single individuals is too small to draw any conclusions, but the curves from the available data show an increase in the concentration at the

middle of the menstrual cycle and just before menstruation (fig. 1). This finding is in keeping with studies on the urinary excretion of estrogens and with the results obtained by Fluhmann with the mucification test.

It is probable that the greatest advantage of this procedure lies in the fact that it may be used successfully with as little as 5 cc. of blood. In a previous study it was possible to analyze the estrogen concentration of the blood of women at four-hour intervals during the course of 24-hour periods (20). However, it is also adaptable to the investigation of the hormone content of whole blood, serum and cells, since this separation may be easily secured by centrifugalization and pellets made from each of the constituents. This approach already has shown a distinct difference between the blood of normal non-pregnant as compared with pregnant women. In the non-pregnant state the estrogenic hormone concentration of blood serum and blood cells was found to differ markedly in that the blood cells contained twice or more rat units per unit volume than the blood serum (21). On the other hand, a similar study with pregnant women failed to show any such discrepancy and both serum and cells showed a corresponding potency per unit volume of the blood constituents (22).

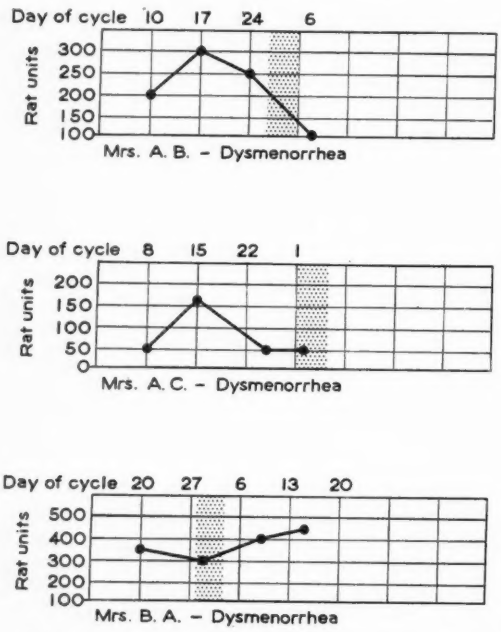

Fig. 1. Blood estrogenic hormone determinations by the method of intravaginal application. Specimens from A.B. and A.C. were examined after acetone-ether extraction and from B.A. by the use of pellets.

SUMMARY

A modification of the Allen-Doisy test for estrogenic hormone is described. It is based on the intravaginal application of material and is a very sensitive procedure. It has been used to study the estrogen content of the blood of women. Acetone-ether extracts were first employed, but higher values were obtained with the use of pellets made from desiccated blood.

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The Distribution of Estrogens in the Blood of Pregnant and Non-pregnant Women[1]

[Blood Estrogens]

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IN A PREVIOUS COMMUNICATION (1) it was shown that the estrogenic hormone content of blood cells from non-pregnant women is twice or more than that of blood serum when compared per unit volume. The present study deals with an analysis of the amounts of estrogen demonstrable in the (*a*) serum, (*b*) red cells, and (*c*) a mixture of red and white cells in the blood of women during various stages of gestation as well as in non-pregnant individuals.

TECHNIC

The details of the test employed in this study have been given in a separate report (2). The blood was obtained by venapuncture and separation of the cells and serum was accomplished by centrifugalization. Each constituent was measured and placed in a cellophane tube suspended in air and exposed to an electric fan at room temperature. In a few hours complete desiccation occurred. The resultant powder was then weighed in order to compare with the volume originally employed. After the addition of 10% of sesame oil the powder was made into small compressed pellets weighing from 8 to 80 mg. each. The biologic assay of the pellets was conducted by inserting them into the vagina of standardized spayed adult white rats in the manner previously described. Three rats were used for pellets of similar weight. The results were considered positive when two of three animals showed cornification in 52 or 62 hours.

An exact separation of red and white blood cells is not possible by simple laboratory procedures, but it is well known that after spontaneous clotting most of the white cells are found in the layer above the clot and immediately subjacent to the serum. In this way it was possible to divide the clot and compare the hormone content of red cells alone and a mixture composed of red cells plus most of the white cells. When this procedure was employed the clotted material was measured, desiccated in the manner described above, weighed, and analyzed according to the modified Allen-Doisy test used in this study.

TABLE 1. DISTRIBUTION OF ESTROGENIC SUBSTANCES IN THE BLOOD OF PREGNANT WOMEN

Patient	Month of Gestation	R.U. per 100 cc.	
		Blood serum	Blood cells
DA	2	400	360
DB	4	450	400
DC	4	600	500
DD	5	400	>370
DE	5	600	500
DF	6	600	500
DG	6	650	>500
DH	7	1,000	900

TABLE 2. DISTRIBUTION OF ESTROGENS IN THE BLOOD OF PREGNANT WOMEN

Patient	Month of Gestation	R.U. per 100 cc.		
		Blood serum	Red blood cells	Mixture of R.B.C., W.B.C.
EA	1	250	350	>350
EB	2	300	>400	>400
EC	6	600	500	>400
ED	7	<800	650	700
EE	8	400	>600	>700
EF	9	600	>650	>700

RESULTS

The results are given in the accompanying tables, and three observations have been made.

(*a*) In non-pregnant women the blood cells contain twice or more estrogenic hormone per unit volume than the serum (1), but from table 1 it is seen that this

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[2] John Simon Guggenheim Fellow.

does not hold true during gestation. A slight difference was shown in most cases but it is felt that this is not significant and can be explained by variations consistently found in biologic assays. This observation corroborates the report of Kemp and Bjergaard (3) and may prove of importance in the study of various pathologic conditions occurring during pregnancy.

TABLE 3. DISTRIBUTION OF ESTROGENS IN THE BLOOD OF NON-PREGNANT WOMEN

Patient	Clinical Diagnosis	Day of Cycle	R.U. per 100 cc.		
			Blood serum	Red blood cells	Mixture of R.B.C., W.B.C.
FA	Metrorrhagia	13	300	500	500
		20	200	>420	400
FB	Sterility	1	240	380	>420
		8	220	390	370
FC	Dysmenorrhea	15	350	480	520
FD	Amenorrhea		200	450	430
FE	Oligomenorrhea	3	150	>380	>380
		10	>140	>300	300
FF	Menorrhagia		200	370	410
FG	Climacteric		>170	>430	>450
	(Pooled specimens)		>200	450	430
			230	380	500

(*b*) A second group of pregnant women was examined and an attempt made to separate the white blood cells from the red cells. The results given in table 2 show no significant difference in the estrogenic hormone content of the blood serum, red blood cells and the mixture of red and white blood cells.

(*c*) The high concentration of estrogens in the cellular constituents of the blood of non-pregnant women naturally led to the question as to whether the red or white cells were responsible. For this reason a number of specimens from non-pregnant women with various gynecologic disturbances were studied. The results corroborate the previous observation that blood cells in non-pregnant women have a greater amount of estrogenic hormone per unit volume than serum, but no significant difference was observed in the comparison of red blood cells and the mixture of red and white cells (table 3).

SUMMARY

In non-pregnant women the blood cells contain twice as much or more estrogenic hormones per unit volume than the blood serum.

During pregnancy estrogenic hormones were found equally distributed between the blood cells and the blood serum.

No significant difference in the amounts of estrogen present in red blood cells and in a mixture of red and white blood cells was observed in either pregnant or non-pregnant individuals.

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The Control of Menopausal Symptoms with Estradiol Benzoate

Impressions Gained in Treating a Group of Forty Patients

[Menopause]

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While the element of physio-pathological variation is recognized in all applied forms of therapy and results in the chronic but needful caution to 'individualize' patients it is nowhere more apparent than in the use of endocrine substances for various biologic deficiencies. It is particularly true in treating patients with menopausal symptoms as is demonstrated in this study of forty menopausal patients under conventional estrogenic treatment. These cases were of varying symptomatologic severity and represented both physiologic and artificial types of menopause.

The therapy the patients received, the dosages of hormone employed, and the results obtained have been recorded and are presented in tabular form. Close scrutiny of the cases listed will show that it is not always possible or wise to recommend specific doses for patient-groups with menopausal symptoms. However, it is possible to place these patients in two categories and then, recognizing the latitude of biologic needs, to offer a therapeutic scheme which will suit most and can be altered as needed. In addition to the necessity of individualizing the treatment of patients, a second thing which this study has brought out is the fact that in certain respects estradiol is superior to estrone in relieving menopausal symptoms.

The data in table 1 concern the use of estradiol benzoate[1] in 40 menopausal cases. Eleven of these menopausal syndromes were artifically induced by operation.

In this study the term average was used when the menopausal symptoms, while of moderate or severe degree, did not interfere with the patient's usual living habits, social or domestic obligation, and did not produce obvious and persistent mental depression. The cases regarded as severe were those in which the severe symptoms were associated with physical and/or mental prostration. Of the 26 cases of natural menopause, 4 were of the severe type. Of the 11 cases of postoperative menopause, 6 were severe.

The dose of estradiol benzoate usually given in the average case was 2,000 R.U. twice a week until there was a definite abatement or amelioration in the symptoms, following which the same dosage was continued at weekly or bi-weekly intervals for 2 or 3 months. At the end of this period a maintenance therapeutic dose was determined by the response of the patient and the time interval elapsing between the injected dose and the recurrence of symptoms. Injections were then continued at intervals one week shorter than the time thus determined.

In severe cases, the initial dose of estradiol benzoate was 6,000 R.U. repeated at intervals of 4 to 8 days. Further dosage was determined by the response and freedom from symptoms, an attempt being made to reduce both the amount and the frequency of therapy.

The outstanding symptoms were hot flushes, nervous irritability, night sweats, and insomnia. Other complaints noted were acne, not previously present and appearing with onset of menopausal symptoms, headaches, fainting and dizzy spells, actual syncope, and recurrent nausea.

The most severe symptoms were noted in the cases of menopause induced by operation. This menopausal syndrome, similar to physiologic menopause in symptomatology but more severe, occurs irrespective of the age of the patient at the time of a castrating operation, providing she had not previously experienced a cessation of menopausal symptoms. Apparently, small amounts of residual ovarian tissue are sufficient to prevent the onset of these symptoms, even though there has been a total ablation of uterine tissue. My operative and clinical experience does not bear out the frequently-mentioned occurrence of rapid atrophy and dysfunction of ovarian tissue fol-

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[1] The preparation used was Dimenformon Benzoate, generously supplied for this study by Roche-Organon, Nutley, New Jersey.

TABLE 1. ESTRADIOL BENZOATE IN TREATMENT OF THE MENOPAUSE[1]

Case No.	Age	Symptoms[2]	Previous Therapy (Estrone parenterally except as indicated) Dosage I.U.	Duration mo.	Interval wks.	Estradiol Therapy Duration mo.	Interval wk.	Comparative Results with estradiol[4]
EARLY MENOPAUSE								
3	38	M	10,000	4½	1–3	6	4	+
23	43	S	10,000–30,000	8	bi-weekly	6	1–2	+
24	42	M	P.O. ext.[3]	2	1	5	2	Very good result
34	37	M	P.O. ext.[3]	12	½ to 1	5	1–3	Well controlled quickly
35	41	S	10,000	24	4	16	8–12	+
MENOPAUSE								
2	44	S	10,000	24	½–1	4	1–3	Much longer effect
4	46	M	10,000	12	1	9	3	Better, with longer effect
5	43	M	10,000, P.O. ext.[3]	17	4	8	6	+
9	48	S	10,000	10	2	12	1–4	+
10	41	S	10,000	6	2–6	8	2–12	4,000 R.U., 1 dose every 3 mos. now adequate
12	50	M	10,000	2	2	9	8	+
13	48	S	10,000	2	1–2	12	2–4	Severe symptoms rapidly controlled
14	44	M	10,000	3	1–2	6	1–4	Marked improvement
15	51	S	10,000	14	2–3	12	2–12	Symptom free for 3 mo.
16	47	M	10,000	24	2	10	2–4	+
25	48	S	10,000, P.O. ext.[3]	8	2–4	14	4	No symptoms for 9 wks. after 1st injection
26	48	M	10,000	12	3–4	8	2–3–7	Much better
27	41	M	10,000, P.O. ext.[3]		irregular	6	2	+
28	57	S	P.O. ext.[3] 10,000	48	2–4	12	2–10	+
29	43	S	P.O. ext.[3]	1	½–1	4	1	Rapid subsidence of all symptoms
30	42	M	10,000	12	3 wks.	6	3	Rapid effect
31	50	M	P.O. ext.[3]	12	5	12	3	+
33	45	M	10,000	12	4	6	2–12	Very good results
37	53	M	10,000–30,000	9	2–8	6	1–4	Much better
38	39	M	10,000–30,000	6	2–3	12	20	Much better with longer effect
39	44	S	—	—	—	6	6	Unsatisfactory and inadequate
40	48	M	—	—	—	8	4	Periods resumed normal characteristics
POST-OPERATIVE MENOPAUSE								
6	40	S	—	—	—	12	2½–6	+
7	48	S	10,000, 30,000	20	2–4	12	3 (8 between inj. 1 and 2)	No difference
8	50	S	10,000	9	2–3	12	2–8–4	+
11	41	M	—	—	—	9	6	+
17	51	S	10,000	12	1–3	12	4	Initially worse flushes, then nearly complete relief
18	57	S	10,000	26	1–3	12	2–5	Symptoms fairly well controlled
19	39	M	10,000	3	2	9	8	Symptoms fairly well controlled
20	37	M	10,000	2	2	12	6	One 12-wk. lapse of symptoms
21	48	M	10,000	½	2	9	3–8	Well controlled
22	40	S	10,000–30,000	6	bi-weekly	8	1–3	Well controlled
32	47	S	30,000	7	7	4	1–2	Estrone much more effective with this patient
36	53	S	10,000	12	4–6	12	1–3	No improvement until 5th injection; then much better
POST MENOPAUSAL								
1	66		10,000	4	1	2	1	Marked symptomatic improvement

[1] Dosage in mild cases 2,000 R.U. twice a week until improvement established, continued at weekly or bi-weekly intervals thereafter for 2–3 months before maintenance dose established. In severe cases initial dose 6,000 R.U. repeated at intervals of 4 to 8 days.

[2] M, mild; S, severe.

[3] P.O. ext.; Pituitary-ovarian extract (Breon), not standardized, in dosage of 1 to 2 cc. weekly, either alone or with estrone as indicated.

[4] + Indicates symptoms were better controlled with estradiol than with previous therapy.

lowing removal of all uterine-mucosa-bearing tissue.

Of these 40 patients with menopausal or postoperative menopausal symptoms, 26 had been previously treated with estrogens of various types. These patients, in addition to 14 others who had not previously had estrogenic therapy, were given the equivalent dosages of estradiol benzoate in an attempt to evaluate the relative effectiveness of the different types of estrogens for similar conditions and symptoms. An attempt was also made to determine the value of estradiol benzoate in relieving the symptoms, with respect to the amount employed and the frequency of the injections.

While oral therapy had been used in a considerable number of cases, its effects were so varied and indeterminate that no opinion is offered concerning its value during the period of observation entailed in the present study.

The patients who had been on other forms of estrin therapy were not informed that the type of medication had been changed, in order to reduce the psychic factor of individual interpretation of results.

It was found that patients suffering menopausal disturbances could be relieved of such symptoms by using an estrogenic substance hypodermically, provided an adequate dose was used. Obviously the adequate dose varied in each instance and in amount from 2,000 R.U. every 2 weeks to 6,000 R.U. twice a week. Estradiol benzoate did not possess any peculiar quality which made it more specific for menopausal symptoms than any other estrogenic preparations, but it was observed that patients receiving estradiol therapy could be placed, after a period of from 2 to 4 weeks, on a maintenance dose which was similar in amount but less frequent in its administration than had hitherto been possible.

While the menopausal symptoms are fairly constant in character, the individual variations, as expressed in terms of the comfort of the patient, are so great that each presents an individual problem for which no single formula of therapy can suffice. This is probably best illustrated by the following case histories.

Case 8. R. F. Age 49. Hysterectomy performed for fibroid uterus with profuse hemorrhages. There were no menopausal symptoms noted prior to operation. Four months later the patient began to have hot flushes, recurring at weekly intervals and followed in a month by recurrent flashes and night sweats of sufficient degree to wet the bed clothing. B.P. rose from the previous level of 144/86 to 176/90. Weight remained constant.

She was given estrone, 10,000 I.U. at weekly intervals and the condition was kept under control. After 3 months the intervals between treatments were extended to 3 weeks with recurrence of flushes and "rushes of blood to the head." Upon establishing a two-week interval for injections all of her symptoms were kept under control. On July 2, 1940 estradiol benzoate was substituted for the form of estrogen previously used. After 3 months it was possible to reduce the biweekly injections to every 3 or 4 weeks and still maintain freedom from symptoms. In the meantime the blood pressure had dropped, ranging from 150 to 166, systolic, and 78 to 84, diastolic.

Case 2, A. A. Age 42. Seen in 1938 because of nervous headaches, marked general nervous irritability, insomnia, and mental depression. Her menstrual periods were regular with a 28-day cycle. Except for a moderately severe degree of secondary anemia she had no other physical findings of note. Within the subsequent 3 months she was hospitalized twice because of an exaggeration of the psychic symptoms. She had a fixed idea that she was about to die, numbness in the extremities, feelings of profound exhaustion, sensitive areas along the course of her spine, chilly feeling and sweats especially at night. Her symptoms seemed to be exaggerated at the time of her periods. In conjunction with other therapy, which was soon discontinued, she was given 10,000 I.U. of estrone at intervals of 4 to 7 days. There was marked improvement in her general condition within a month and she seemed to get progressively better. The symptoms recurred upon deferring or omitting estrone therapy. On three occasions to determine if the psychic factor of injection therapy was responsible for her improvement, hypodermic medication of other than estrogenic types was employed. In each instance the patient returned complaining of a recurrence of the syndrome for which she had been initially treated. This patient has been on a maintenance dose of estrone therapy at three-week intervals for 2 years and she remains completely well as long as therapy is continued; the only breaks in her feeling of well-being have been at the times when estrone therapy was stopped or replaced. In this instance estradiol benzoate, employed over a period of the past six months, has been as effective as other types of therapy.

Case 22, H. D. Age 41. Operation April, 1937 with panhysterectomy for fibroids and bilateral ovarian cysts. Preoperatively, there were no symptoms which could be ascribed to ovarian deficiency other than severe nervous spells 6 months prior to operation, and insomnia. There were no symptoms for 3 months postoperatively when there appeared a sequence of night sweats, "nervous shakes," and hot flushes, the latter of a progressively severe type. Injections of 5,000 and 10,000 I.U. of estrone at 3 day intervals were of no value. She was then given 30,000 I.U. every 3 days for 3 doses with prompt relief, following which the interval was lengthened to one week. An attempt 2 months later to reduce the dose was followed by such a severe recurrence of symptoms that 40,000 I.U. of estrone were required to give her relief. The dosage of 30,000 I.U. per week was then resumed for 3 months following which it was reduced to 20,000 I.U. weekly for 2 months and the interval was then lengthened to 2 or 3 weeks. There were recurrences of severe emotional imbalance, mild sweats during the day and severe night sweats with occasional nausea which necessitated increasing the dosage from 30,000 to 45,000 I.U. at such times. This severe menopausal state lasted for 2½ years after

which only occasional dosages of 10,000 to 30,000 I.U at monthly intervals were required. This case represents a severe form of postoperative menopausal syndrome.

SUMMARY

The study has emphasized the necessity of individualizing the treatment of the patient with menopausal symptoms and of adjusting the estrogen dosage to the particular case, not only in the beginning of treatment but also throughout the active and maintenance phases of therapy. Although typical menopausal symptoms can usually be relieved by any estrogen, provided the dosage is adequate, the use of estradiol benzoate appears to have a decided advantage over estrone in that it may be injected less frequently and still control the symptoms and the patients may be placed on a maintenance dosage more quickly. In addition, following therapy with estradiol, the patients in this study seemed to respond satisfactorily to maintenance doses which were administered at much longer intervals than had been possible with estrone.

The Management of Primary Amenorrhea in Hypopituitarism

[Amenorrhea]

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THE MANAGEMENT of functional primary amenorrhea has always been an imposing problem particularly when associated with marked hypopituitarism. Many clinicians question the advisability of treating a persistent primary amenorrhea since the establishment of autonomous function cannot readily be expected with the available means of therapy (1–4). It is noteworthy that cases of this type are seriously handicapped both psychologically and sociologically. There is a persistent request and need for any treatment, regardless of its limitations, which might enable these patients to cope with their handicaps.

Cyclical uterine bleeding or menstruation can be induced in any type of functional amenorrhea with adequate dosage of estrogens and progestogens (5–9). Such therapy, while only substitutional, is usually accompanied by changes in the psychological status and secondary sex characteristics which are of the utmost importance.

The following report is presented to indicate how such cases can be managed over long periods of time by the employment of estrogens and progestogens. Pellet implantation as a source of estrogen, complemented by oral progestogen, is introduced as a simple and effective means of treatment.

The diagnosis of hypopituitary sexual and growth infantilism—the Lorain-Levi syndrome—was established by clinical and laboratory study. A case of delayed puberty is included for contrast and emphasis.

CASE REPORTS

Case 1. M. S., aged 27 (fig. 1), entered the clinic at the age of 15 because of inadequate growth, sexual underdevelopment, amenorrhea and obesity. The history was irrelevant except for meningitis at the age of six. Physical examination revealed a short, underdeveloped girl with no secondary sex characteristics. Scoliosis and lordosis were marked. Blood pressure was 118/64 and the remaining examination was negative. The height was 56¾ inches and the span 56 inches. An intelligence quotient test indicated the upper limit of dull normalcy. The B.M.R. was −6%. The glucose tolerance and the sella turcica were within normal limits. Roentgenograms of the chest

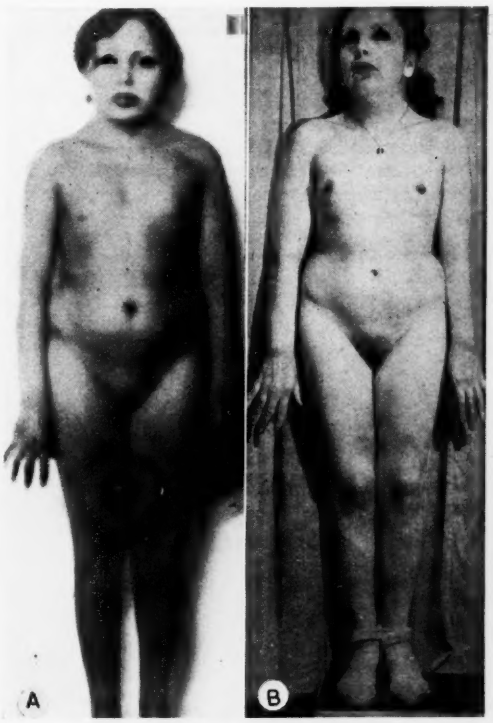

Fig. 1. *Patient M. S., case 1.* A, aged 24; marked infantilism. *B*, aged 27; after two years of therapy.

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1 and 2		3		4		5		6		7	
1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4	
PMS-12	PMS-12	eB-6	eB-6	eB-6	Ae-4	Ae-4	Ae-6	eB-6	eB-6	Ae-3	Ae-4
			Pr-40		Pr-40		Pr-30		Pr-40		Pre-20
menses	days			3		4		6		5	

8		9		10		11 and 12		13		14	
1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4	
Ae-3	Ae-5	Ae-4	Ae-6	Ae-4		PMS-12	PMS-12	eB-6	eB-6	Ae-3	Ae-4
	Pre-30								Pre-40		Pre-40
3		5			2					4	

15		16		17 and 18		19		20		21	
1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4	
eB-4	eB-4	eB-4	eB-4	eB-4	eB-4	90 mgm. pellet implanted					
	Pre-40		Pre-30				Pre-40		Pre-40		Pre 40
3		4		3			3		3		

22		23		
1 2 3 4		1 2 3 4		1
	Pre 40		Pre 30	
3		3		3

eB – Estradiol benzoate. Each dose = 10,000 R.U.
Ae – α estradiol, orally. No. = Mg./day. 1 Mg. = 1200 R.U.
Pr – Progesterone. No. = Mg. injected in 2 weeks.
PMS – Pregnant mare's serum. Each dose = 400 I.U.
Pre – Pregneninolone. No. = Mg./day.

Chart 1. EACH LARGE BLOCK REPRESENTS CONSECUTIVE 4-WEEK PERIODS, WITH 1-WEEK SUBDIVISIONS AS INDICATED. *Case M. S.*

showed evidence of moderate coarction of the aorta. The epiphyses at the wrist were still open. Therapy at that time consisted of thyroid, pituitary growth and gonadotropic extracts and several courses of x-ray irradiation to the pituitary region. After 10 years there was a gain of 2 inches in height and a closure of the epiphyses. Amenorrhea persisted and, except for some pubic and axillary hair, there were no secondary sex characteristics.

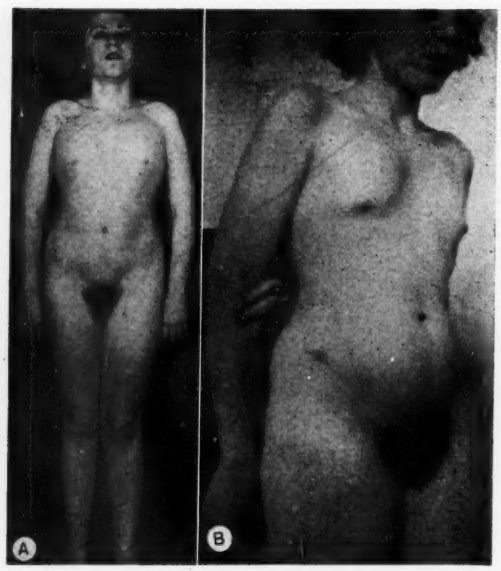

Fig. 2. *Patient M. D., case 2,* A, aged 20; note body configuration and complete absence of breasts. *B,* aged 24; after 1½ years of therapy.

The patient was employed as a secretary since the age of 20. She commented that the absence of breasts and menstruation more than the lack of height made her feel totally unlike other women. Therapy was instituted as shown in chart 1. Cyclical uterine bleeding was regularly secured with each adequate course of therapy. Breast tissue appeared. The body contours approached more feminine lines and the patient reported great improvement in her sense of well being, self-confidence and optimism. There was considerable gratification over the appearance of the 'periods,' even though their dependence on continuous therapy was explained. After two years of therapy the patient has a much clearer understanding of her physiological problem, as well as the dependence on therapy for the maintenance of 'menstruation.' We have established no time limit for the treatment in this case but hope to adjust the patient to her problems, supported by the progress achieved. The use of pellet implantation and periodic oral progesterone has given her further detachment from the need of constant attention. The patient, to this point has had five 'periods' from one implantation. Including these, there has been a total of 16 periods of bleeding during the course of treatment.

Case 2. M. D. (fig. 2), aged 24, was admitted to clinic in 1933 at the age of 16 because of inadequate growth and amenorrhea. The past and family histories were irrelevant. Physical examination showed a short, sexually underdeveloped girl with an apparent age of about 10 years. No breast tissue was palpable and the external genitalia were infantile. There was a moderate amount of pubic hair. Rectal examination revealed a small uterus. The height was 56½ inches and the weight 101 pounds.

The basal metabolic rate was −30%. A glucose tolerance test gave values of 70 mg.% fasting, and at ½ hour intervals 107, 78, 90 and 90 mg.% of glucose. The blood cholesterol was 160 mg.% and the urea nitrogen of the blood was normal. X-ray examination showed the sella turcica to be of average normal size and the wrist epiphyses moderately delayed in development. The urinalysis, electrocardiogram and blood count findings were all normal. The blood Wassermann reaction was negative.

At present, this patient offers a most critical problem of psychological and social maladjustment associated with the endocrine dysfunction. While psychiatric control has not been accomplished, the most significant advances were noted during the months of regular cyclical uterine bleedings.

1				2				3				4				5 and 6				7 and 8			
1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
eB-6	eB-6			eB-6	eB-6			eB-6	eB-6			Ae-4	Ae-6							PMS-6	PMS-12		
	Pr-40				Pr-30				Pr-30				Pr-30										
menses	day			4				4				4				3							

9				10				11				12 and 13				14				15			
1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Ae-3	Ae-4			Ae-4	Ae-5			Ae-4	Ae-5								30 mgm. eB implanted						
	Pre-10				Pre-30				Pre-30													Pre-30	
				1				3				2											

16				17				
1	2	3	4	1	2	3	4	1
	30 mgm. eB implanted							
		Pre-40				Pre-40		
				2				

eB — Estradiol benzoate. Each dose = 10,000 R.U.
Ae — α estradiol, orally. No. = Mg./day. 1 Mg. = 1200 R.U.
Pr — Progesterone. No. = Mg. injected in 2 weeks.
PMS — Preg. mare's serum. Each dose = 400 I.U.
Pre — Pregnenindone. No. = Mg./day.

Chart 2. *Case* M. D.

The visual fields showed moderate concentric constriction. The somatic and sexual infantilism confirmed the diagnosis of hypopituitarism of the Lorain-Levi type.

Treatment until 1939 consisted of desiccated thyroid, theelin, chorionic gonadotropin and pituitary growth and gonadotropic extracts. There was no change in the growth or sexual status with this therapy. The patient was becoming increasingly more difficult as a psychological and social problem. She complained bitterly to the doctors and her family that she was underdeveloped, did not menstruate and was not at all like other women. She noted further that no previous treatment had been of help and her despondency led to the threat of suicide.

It was felt at this time that the induction of uterine bleeding and breast development might reverse the effect of the repeated failure of treatment. This was accomplished as described in chart 2. The appearance of menstruation and breast tissue was of immediate psychological value to the patient. She became brighter, more cheerful and amenable to suggestion at home, and decidedly more hopeful. As treatment progressed the Mental Hygiene department assisted in the care of the patient. The procurement of employment, which would have been of great help in adjusting this patient socially, was unfortunately not achieved.

There was evident disappointment and dismay when a 'period' was missed because of omission of therapy or the use of gonadotropes. The successful 'periods' with oral therapy alone were appreciated by the patient since frequent clinic visits were avoided. As indicated in chart 2, the use of 30 mg. of estradiol benzoate by implant was inadequate for any bleeding when used alone and good for only one 'period' when complemented by oral progesterone.

Case 3. A. M., aged 19. This patient was first observed in the clinic in 1937 at the age of 15 for amenorrhea and slow growth. There was no relevant past or family history. Examination revealed a sexually and physically underdeveloped girl with no secondary sex characteristics. The height was 53¼ inches and the weight 79¼ pounds. The basal metabolic rate was +8%. Electrocardiogram, urinalysis, and blood chemistry findings were all normal. Blood Wassermann reaction was negative. The sella turcica was 40% undersized by roentgenogram. Psychiatric study revealed some mental retardation. Irregular treatment during the next two years with thyroid and pituitary growth and gonadotropic extracts was followed by a gain of one inch in height and the appearance of a small amount of pubic hair. There was no breast development and the amenorrhea persisted.

Treatment with the sex steroids was begun in 1939 at the age of 17, as indicated in chart 3. The induced bleeding was accompanied by good breast development and the body contour approached a more mature feminine type. The results were keenly appreciated by the patient, and any lapse in therapy or an unsuccessful cycle brought the demand for the same treatment that had previously been effective.

The patient is now 19 years old and somewhat backward mentally. She is satisfied with the oral therapy and refuses pellet implantation. The present problem is to maintain the psychological incentive that has been gained and to develop an outlet, preferably manual work, for her level of intelligence. We believe that her previous absorption in the menstrual failure has been adequately elimi-

nated and can be controlled as long as is necessary, leaving the patient free to concentrate on work.

At one point during treatment an appendectomy was performed. Pelvic exploration revealed a small uterus but the ovaries could not be palpated.

Case 4. P. M., aged 19. A 16-year-old high school student was referred to the clinic in 1938 because of somatic and sexual underdevelopment and amenorrhea. The mother was a diabetic and 48 years of age when the patient was born. Five siblings were normal. There had been little growth since the age of 8 years. There was a complete absence of secondary sex characteristics except for a minimal amount of breast tissue. The appearance was that of a 10-year-old child. The blood pressure was 84/60. The height was 51 inches, the span 52¼, upper measurement 24½ and the lower 26½ inches. The weight was 59 pounds. The basal metabolic rate was −2% and the sugar tolerance test indicated a fasting blood sugar level of 60 and after one and two hours 85 and 50 mg.%. The visual fields, urinalysis, and the sella turcica were all normal. The Wassermann reaction was negative. The diagnosis was hypopituitarism of the Lorain-Levi type. The treatment during the next 18 months consisted of several courses of injections of pituitary growth hormone preparations and thyroid to tolerance. In this time the patient gained 2½ inches in height and there was a slight increase in breast tissue.

Since we believed that a spontaneous menarche would not occur and the patient was depressed by the persistent amenorrhea, estrogen and progestogen therapy was instituted as indicated in chart 4.

As a result of the patient's confusion in following directions, the bleeding episodes were irregular at first. However, the breasts quadrupled in size very rapidly and the patient was delighted and encouraged by the appearance of bleeding periods. As a means of simpler handling, estradiol benzoate pellets were implanted as indicated in the chart, and bleeding appeared with this therapy. Epiphyseal, genital and psychiatric changes are being followed. The patient now uses facial make-up freely and has evinced a shy interest in boys. She helps at home with the housework and her family is just as pleased with the improvement as is the patient. We have noted the transition from a sullen child to a rather impish but happy young girl. This patient's temperament has been so definitely improved that we are comparatively certain of a successful psychological adjustment.

Case 5. I. B., aged 19, was admitted to the clinic in 1936 at the age of 14 because of inadequate growth and amenorrhea. The family history was irrelevant. The past history

1		2		3 and 4		5 and 6		7		8	
1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4	
eB-6	eB-6	Ae-3½	Ae-4½			PMS-12	PMS-12	eB-6	eB-6	Ae-3	Ae-4
	Pr-30		Pr-30						Pr-30		Pre-20
menses	days	2		4						5	

9		10		11 and 12		13		14		15 and 16	
1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4	
Ae-4	Ae-5	Ae-4		SYN-12	SYN-12	Ae 4	Ae-5	Ae ½		Ae-3½	Ae-5
	Pre-30						Pre-40				Pre-30
		3	4					1			

17 and 18		
1 2 3 4		1
Ae-3	Ae-4	
	Pre-30	
3		3

eB – Estradiol benzoate. Each dose = 10,000 R.U.
Ae – α estradiol, orally. No. = Mg./day. 1 Mg. = 1200 R.U.
Pr – Progesterone. No. = mg. injected in 2 weeks.
PMS – Pregnant mare's serum. Each dose = 400 I.U.
Pre – Pregneninolone. No. = Mg./day.

Chart 3. *Case* A. M.

1		2		3		4		5 and 6		7	
1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4		1 2 3 4	
eB-6	eB 3	eB 3		Ae-4	Ae-5	Ae-3½	Ae 3½	Ae-3	Ae-4	30 implanted	mgm. eB implanted
	Pre 40	Pre 40			Pre-40				Pre-30		Pre 40
menses	days	3				5	2			3	

8		
1 2 3 4		1
	Pre 40	
3		3

eB – Estradiol benzoate. Each dose = 10,000 R.U.
Ae – Alpha estradiol, orally. No. = Mg./day. 1 Mg. = 1200 R.U.
Pre – Pregneninolone (oral progesterone). No. = Mg./day.

Chart 4. *Case* P. M.

indicated that there had been little growth in the previous 5 years.

Physical examination gave normal findings except for the small amount of breast tissue and infantile genitalia. There was little pubic or axillary hair. The height was 54 inches, and the weight was 78 pounds. The basal metabolic rate was −18%. Blood sugar tolerance test results were 77 fasting and 96 and 66 mg.% of glucose after one and two hours. Cholesterol was 155 mg.%. X-ray examination showed the sella turcica and epiphyses to be normal. Treatment during the next two years consisted of desiccated thyroid, pituitary growth and gonadotropic extracts, chorionic gonadotropin and moderate doses of theelin. There was a gain of 4 inches in height and at the age of 16½ years the breasts and secondary sex characteristics appeared rapidly and well. Following no regular form of therapy, the patient spotted consecutively for several months, had one week of menorrhagia that required hospitalization and then had more or less irregular cycles of bleeding. All secondary sex characteristics developed normally. Several courses of pregnant mare's serum and estrogen were used in an effort to regulate the cycles but without apparent effect. The rapid change in the patient's appearance can be judged from the photographs.

This case was included for comparison to stress the occurrence of delayed puberty. The therapy, which was similar to that followed in the preliminary treatment of the previously described cases, probably had little influence on the subsequent clinical course. This is not a result that can be expected in a true case of hypopituitarism of the Lorain-Levi type.

DISCUSSION

The recurrence of cyclical uterine bleeding and the maintenance of secondary sex characteristics was accomplished in our cases by the continuous use of estrogens and progestogens. Since patients with sexual and somatic infantilism are usually acutely conscious of their deficiencies, the psychological encouragement that follows this therapy is of distinct benefit. It is noteworthy that the absence of menstruation and breast development is of more psychological importance than the lack of height.

The ineffectiveness of the gonadotropes used was anticipated. The ovaries, in a true case of hypopituitarism that has existed for a considerable period, are usually atrophic (2). Experimental and clinical work has indicated that it is extremely difficult, if not impossible, to stimulate function in ovaries that have been free of pituitary control for some time. It is possible that when more potent preparations are available, they will be effective; particularly when used subsequently to and concomitantly with the estrogens.

If, after the consideration of a normal delay of puberty, the induction of cyclical uterine bleeding and the improvement of secondary sex characteristics are desired in the hypopituitary state, the use of sex hormones offers the most effective means at present. A preliminary period of treatment with the gonadotropes and thyroid should be instituted in all cases. Administration of the steroids by injection may be advisable to produce the initial changes under direct observation. The oral route eliminates many of the inconveniences to doctor and patient and is equally successful. The large number of tablets to be consumed daily may be an objection to this form of therapy. The most convenient method, which appears entirely adequate, is the use of pellet implantation of estradiol benzoate complemented by oral progesterone. The technique has been adequately described in the literature on testosterone and desoxycorticosterone. The optimum dosage for each implant has not been determined. In our experience to this date, 30 mg. of estradiol benzoate will suffice for not more than one month, and 90 mg. will last at least five months. At first an oral progestogen was used in 30 to 40 mg. doses daily during the second two weeks of each four-week cycle. With that routine the bleeding was premature, and the onset followed a three-week interval. Subsequently, the oral progestogen was only given during each fourth week to maintain the monthly intervals.

It is interesting to note that Gillman, reporting his results in normal female monkeys and humans, was able to produce extracyclic 'progesterone' bleeding with properly spaced adequate doses of progesterone (10). Zondek reported comparable results (11). This bleeding occurred prematurely when given in the middle of the cycle. Progesterone bleeding could be induced only when sufficient estrogen activity was available and was invariably more prompt and regular than the 'estrogen deprivation' bleeding. Supplying a continuous source of estrogen by pellet implantation, it is possible to cause regular bleeding by properly spaced ingestion (or injection) of progestogen. To rely on the irregular estrogen deprivation bleedings would not be desirable. The very promptness and regularity of the periods are a source of satisfaction to the patients. The main effort in treatment is directed toward duplicating a normal, regular phenomenon. The psychological disturbances dependent on the phenomenon appear to follow closely the accomplishment of that end.

CONCLUSIONS AND SUMMARY

Four cases of hypopituitarism of the Lorain-Levi type, with sexual and somatic infantilism, are described and their management charted in detail.

Cyclical uterine bleeding associated with changes in the secondary sex characteristics was induced by the continuous use of estrogens and progestogens.

Parenteral and oral therapy were equally effective. The method of implanting pellets of estradiol benzoate subcutaneously as a source of estrogen, complemented by regularly spaced periods of oral progesterone was considered the most desirable and effective means of handling the therapy which must probably be continued as long as results are desired. When therapy was discontinued or the gonadotropes used, there was no bleeding and the increased breast tissue regressed about 25%.

Pregnant mare's serum and a combination of chorionic gonadotropin and an anterior pituitary gonadotropic extract were ineffective in inducing bleeding or maintaining the secondary sex characteristics in our cases with the dosage used.

The psychological improvement that accompanied the uterine bleeding and development of sex characteristics, particularly of the breasts, was considerable. This aspect alone justifies the treatment, even though no permanent cure can be promised. All cases of this nature should be given the advantage of a trial of therapy during which some psychological adjustment may be possible.

The cost of therapy is still prohibitive. The use of pellet implantation and oral progestogen reduces the inconvenience of the doctor's management to a minimum and allows the patient greater freedom.

It is important that therapy should not be begun before the age of about 17, or at least until delayed puberty has been considered. A case of this type is described for emphasis and contrast.

The following materials were supplied by the Schering Corporation, Bloomfield, N. J., through the courtesy of Dr. Max Gilbert: estradiol benzoate (Progynon-B), alpha estradiol (Progynon-DH), pellets of estradiol benzoate, progesterone (Proluton) pregneninolone (Pranone), and pregnant mare's serum (Anteron).

Pregnant mare's serum (Synapoidin) was supplied by Parke, Davis & Co., Detroit, Mich., through the courtesy of Dr. John Ralston.

We wish to thank Dr. Joseph Eidelsberg, Chief of the Endocrine Clinic, New York Post Graduate Hospital, for his guidance in collecting and arranging this material.

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The Laurence-Moon-Biedl Syndrome

Case Report with Complete Autopsy

[Laurence-Moon-Biedl Syndrome]

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FOR MANY YEARS the etiology of the Laurence-Moon-Biedl syndrome has been a question of very unsatisfactory debate. Its establishment as a diagnostic entity, however, is quite secure with over 100 cases recorded in the literature.

In 1866, Laurence and Moon (1) reported 4 cases of retinitis pigmentosa occurring in the same family. associated with other unusual abnormalities including hypogenitalism, obesity, mental deficiency, and dwarfism. The symptom complex, although observed occasionally by clinicians in the interim, was not recognized as a disease entity until 1920 when Bardet (2) reported an isolated case of polydactyly, adiposo-genitalism, and retinitis pigmentosa. French authors are naturally inclined to associate his name with the syndrome. Biedl (3), in 1922, reported 2 cases in the same family, and he considered that the syndrome in its complete form would include any of such congenital malformations as polydactylism, retinitis pigmentosa, skull deformities, and atresia ani, as well as mental deficiency, obesity, possible genital hypoplasia, and digestive disturbances.

Today most clinicians are alert in diagnosing cases of the syndrome which exhibit the majority, or all of the following: adiposo-genitalism, retinitis pigmentosa, mental deficiency, familial occurrence, and some congenital anomaly, the most frequent being polydactylism and syndactylism. Marmor and Lambert (4) emphasize, however, that it is not necessary to have all of the cardinal signs present in order to make a presumptive diagnosis, the most important being obesity, genital dystrophy, and retinitis pigmentosa.

It is not the purpose of this paper to discuss fully either the history or the clinical manifestations of the syndrome. This has already been done by many authors, perhaps most critically by Cockayne, Krestin, and Sorsby (5) in 1935, and by Sorsby, Avery, and Cockayne (6) in 1938. These authors have made a complete survey of all the reported cases, and they have summarized the various signs and symptoms, presented what little morbid anatomy is available, and discussed the various etiological theories so far advanced.

The major burden of explaining the etiology of the Laurence-Moon-Biedl syndrome has fallen to the lot of the geneticist and the endocrinologist. Since the cases observed resembled the well-known syndrome of dystrophia adiposo-genitalis described by Fröhlich (7) in 1901, and thought by him at that time to be due to pituitary disease, it was believed by many that the Laurence-Moon-Biedl syndrome might also reveal pituitary abnormality. The great majority of the cases reported exhibited nothing abnormal in the region of the sella turcica, either radiographically or symptomatically. Biedl (3), observing this, particularly in his 3 cases, abandoned the hypophyseal theory, and proposed a hypothalmic, or at least a diencephalic lesion. In 1924 Raab (8) suggested that the major lesion was an internal hydrocephalus due to a high or massive dorsum sellae pressing upon the infundibular stalk. In 1932 Ornsteen (9) proposed a developmental defect of the ectopic zone of the prosencephalon as being responsible, and he thought the skeletal malformations were due to an accidental coupling of defective somatic genotypic characters. This theory was challenged since polydactyly probably occurred too frequently to be due to an accidental coupling.

The reason for all this theorizing is of course obvious: no autopsy on a case of the Laurence-Moon-Biedl syndrome had been reported until 1936. Since that time the reports of some 5 autopsies have appeared in the literature and at least 2 of these are incomplete. Unfortunately the lack of uniformity in the morbid changes of these cases has prevented diagnostic correlation. It is also unfortunate that more nearly complete studies of both the central nervous

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system and the endocrine glands were not made in all cases.

Van Bogaert and Borremans (10) reported the first autopsy in 1936. The case was of that of a 29-year-old white male, dying of cardiac failure, who presented the following abnormalities: obesity of face, trunk, and neck, rudimentary genitalia, mental deficiency, bilateral stellate cataracts, bilateral rotatory nystagmus, strabismus, hyperhidrosis of hands and face, short fingers, extensor spasticity of legs, hasty temperament, and central right facial hemiparesis. The members of his mother's family were variously afflicted with mental deficiency and retinitis pigmentosa. The postmortem examination revealed an exostosis of the inner table of the frontal bone, slight enlargement of the sella which contained a normal hypophysis, and slight injection of the pia mater. In the center of the pituitary stalk there was a small, band-shaped, hyalinized area devoid of nuclei. Apparently the autopsy was incomplete since no description of the other organs is given.

The second autopsy was reported later in 1936 by Loepp (11). This was a 39-year-old male who died from esophageal carcinoma. His parents were cousins, and he presented a fairly characteristic picture of the syndrome with the exception of polydactyly.The sella turcica was enlarged and contained a cyst, in the walls of which were epithelial rests. A very small amount of pituitary tissue remained in the stalk. This autopsy apparently also was incomplete, and very little was gained from the descriptive paucity of both this case and the previous one.

The third case was seen by Griffiths (12) and reported in 1938. This was a 7-year-old girl who died of measles. She presented the following abnormalities: dull mentality, symmetrical polydactylism and syndactylism of the feet, obesity, retinitis pigmentosa, nystagmus, and squint. There was a family history of syndactyly and polydactyly, and a brother who died soon after birth presented the same syndrome. At autopsy the uterus, ovaries, and tubes were abnormally small, and the ovaries contained a few primordial follicles. Each kidney showed irregular lobulations of the fetal type with capsular adhesions and thick fibrous bands. The thymus was normal in size but consisted of small islets of thymic tissue, separated by fibrous bands with much fat. There was a scarcity of Hassall's corpuscles. The pituitary was somewhat smaller than usual, particularly the posterior lobe. The anterior lobe revealed great vascularity with numerous prominent sinuses, widely dilated. There was a strikingly high proportion of basophilic cells and a relative paucity of eosinophilic cells. There was no colloid in the pars intermedia. Some congestion was noted in the pituitary stalk. The brain revealed small hemorrhages, congestion, and thrombi of small vessels. There was some diminution in the volume of the gyri, and the frontal poles were shrunken. Sections taken from the base of the brain showed an abundance of small nerve cells, more numerous toward the pituitary stalk. The tuberal nuclei in the hypothalamus contained fewer large cells than normal.

In 1938 Riggs (13) discussed briefly the post-mortem findings in 2 cases of the Laurence-Moon-Biedl syndrome. Recently she has very kindly sent the writer the pertinent clinical and autopsy findings (14). Both cases were males, aged 24 and 19, showing various signs and symptoms of the syndrome. The older died in convulsions. The general autopsy findings were not remarkable except for defective development of the aortic cusps, and the presence of a double right coronary artery. The second revealed hypoplasia of the aorta, kidneys, prostate, pancreatic islets, and interstitial cells of the testes, without mature spermatozoa. A chronic glomerulonephritis was also present.

In both cases the brain was normal in size and appearance. However, in both cases there was a diffuse reduction in ganglion cells, and a predominantly astrocytic gliosis, most marked in the marginal and subependymal regions. There was a marked fibrosis of the blood vessels of the brain in each case. The muscular coats of these vessels were defective in development and in the lumina of the larger vessels myomatous nodules were seen, not only in the hypothalamus, but also in the cerebrum. The subependymal veins showed some enlargement and mural thickening. In the first case there was almost complete loss of cells in the pallidum with an increased number of macrophages filled with blood pigment. In the second case there was a decrease in the number of pallidal cells with astrocytic proliferation; some calcification was noted in the vessels. In neither case did the hypothalamus or diencephalic areas appear to be abnormal in structure.

Additional information includes the gross description of a normal brain in a single case by Bauer (15) in 1927. No microscopic sections were made. Weingrow (16) reports a case in 1936, not autopsied, but studied by ventriculography and encephalography which showed marked cortical atrophy, hydrocephalus, and increased intracranial pressure. The patient apparently was not a very typical case of the Laurence-Moon-Biedl syndrome. In 1938 Stewart (17) reported a case of a possibly related infundibulotuberian syndrome in a 16-year-old boy showing pseudo-hermaphroditism, adiposity, polyuria, and hyperglycemia. There were chronic degenerative changes in the hypothalamic nuclei. A most interesting finding included a marked excess of eosinophilic and basophilic cells in the pituitary gland.

CASE REPORT

The following report includes the clinical findings, the course, and autopsy findings in a 15-year-old Greek boy who presented a rather typical Laurence-Moon-Biedl syndrome consisting of adiposity, hypogenitalism, polydactylism, moderate mental deficiency, bilateral congenital cataracts with blindness, and bilateral genu valgum. Although retinitis pigmentosa was suspected its presence could not be proven because of the presence of cataracts which prevented adequate visualization of the fundi. The consulting ophthalmologist could only suspect the retinal degeneration in the presence of blindness without complete lenticular opacity. Unfortunately permission to examine the eyes at autopsy was not obtained.

Clinical Summary. The patient was admitted to the Medical Service on 8/10/38 with the complaints of nervousness and failing vision of 3 years' duration. He had been seen 5 years previously on the Urology Service at which time his complaints had been enuresis, moderate polydipsia, polyuria, and nocturia. According to his mother's statement he had always been obese and had never had good vision.

Physical examination on first admission had revealed typical adiposo-genitalism with prominent breasts and considerable subcutaneous fat on the chest and abdomen. The genitals were definitely hypoplastic, the penis being equal in size to that of a boy of 2 or 3 years, with a second degree hypospadius. Both testicles were felt in the scrotum although their size was infantile. There was a long redundant foreskin and marked chordee. The urinalysis findings were normal; the specific gravity of the urine was 1.008. The impression of the urologist was enuresis, possible pituitary disease, and genital hypoplasia with hypospadius. No treatment was outlined at the time.

Following discharge the low-grade polydipsia, polyuria, and enuresis disappeared within 1 year. When the patient was admitted on the Medical Service 5 years later complaining of nervousness and failing vision, the following further details were elicited. He had exhibited progressive personality changes since last seen, and was now considered a "gibbering idiot" by his parents. A local physician had told the parents 4 months earlier that he had "bad kidneys, anemia, and high blood pressure."

The family history was not remarkable. Both parents were small and no consanguinity was admitted. The patient had 2 half-brothers, and 1 half-sister, all apparently of normal size, intelligence and vision.

The patient's past history included obesity and impaired vision since infancy. There were no admitted diseases. The boy had had occasional mild frontal headaches, some anorexia, rare constipation, and great desire for sweets. It was stated by his mother that he had had supernumerary sixth digits removed from the hands and feet at the age of two years. He had progressed to the sixth grade in school when his progressive blindness necessitated withdrawal.

Physical Examination. Temperature 37.3°C. (99.1°F.); pulse, 120; respiration, 24; B.P., 150/80. He was a moderately obese boy of 15, uncoöperative, lying restlessly in bed, talking and shouting incoherently in a rambling high-pitched tone. His obesity was of feminine type, with increased padding of the trunk and no apparent excess trochanteric padding. There was a small abdominal panniculus and the breasts were prominent. Facial and axillary hair were not present and pubic hair was feminine in distribution (figs. 1 and 2). The skin had the olive tint characteristic of his ancestry. There were no abdominal striae. On the hands and feet amputation scars were seen where supernumerary digits had been removed. The hands and feet were short and spade-like (fig. 3), and there was a marked genu valgum bilaterally. The penis was rudimentary, 4 cm. in length, with a post-coronal congenital hypospadius, chordee, and a long redundant foreskin (fig. 4). Both testes were in the scrotum, small and firm, and measured 2 cm. in length. By rectal examination the prostate gland could not be felt. The body measurements were as follows: height 65.5 inches; weight 129.5 pounds;

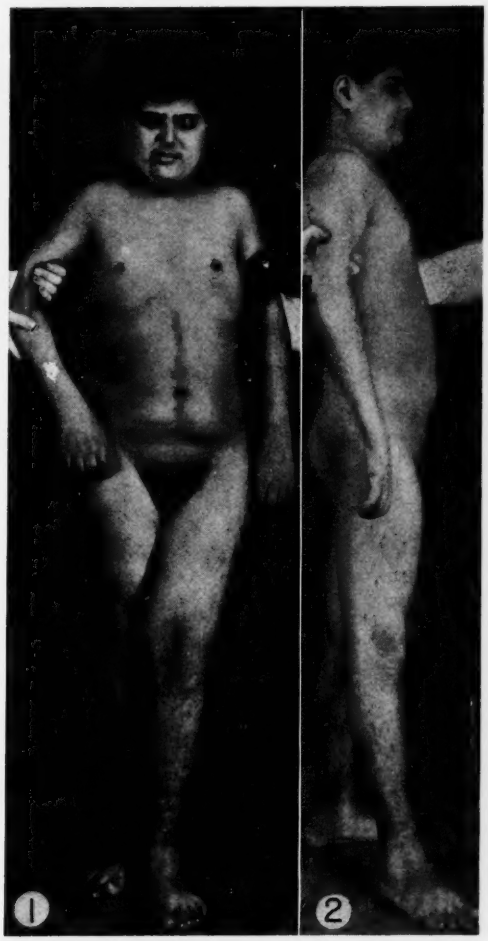

Fig. 1, 2. PATIENT WITH LAURENCE-MOON-BIEDL SYNDROME
Note obesity, genu valgum, genital hypoplasia, and amputation scars where accessory digits have been removed.

span 65 in., upper measurement 32.0 in., lower measurement 33.5 in., head circumference 21.5 in., chest 33.0 in., waist 32.0 in., and hips 33.0 in. Compared with Engelbach (18) standards the only significant variation was 16 pounds weight excess disposed largely on the trunk.

The eyes revealed moderately bluish sclerae and bilateral lenticular opacities. The pupils were widely dilated and reacted poorly to light; accommodation and extra-

Fig. 3. LEFT HAND OF PATIENT. Note amputation scar and contour of fingers. Fig. 4. GENITALIA. Note hypoplasia and hypospadius.

ocular movements could not be elicited. There was no nystagmus. Through the cataracts the fundi appeared pale grey, but the vessels and discs could not be well outlined. There was slight evidence of light perception. The reflexes were equal but hypoactive.

Accessory Clinical Data. Hgb. 7.9 gm., R.B.C., 2,490,000; W.B.C., 11,680. The differential count was 83% polymorphonuclears, 3% large lymphocytes, 5% small lymphocytes, 4% eosinophils, 2% basophils, and 3% monocytes. There were 0.4% reticulocytes and no nucleated erythrocytes. Urine specific gravity was 1.010; albumin, 1 plus. There was no sugar or acetone and no sediment. Wassermann and Kahn reactions were negative on blood serum. Lumbar puncture showed an initial pressure of 260 mm. of fluid with normal dynamics, negative Pandy reaction, and negative Wassermann and colloidal mastix. Although the patient was uncoöperative the basal metabolic rate was −19%.

There was no excretion of intravenous phenolsulphonephthalein dye in the urine in 1¾ hours. A blood culture was sterile. Blood chemistry findings were: glucose 93 mg.%; chlorides 598 mg.%; cholesterol 190 mg.%; negative van den Bergh; uric acid 11.4 mg.%; non-protein nitrogen 127 mg.%; calcium 5.5 mg.%; phosphorus 10.5 mg.%; total protein 6.9 gm.%; albumin 4.1 gm.%; globulin 2.8 gm.%; A/G ratio 1.5. Two glucose tolerance tests showed the diabetic type of curve rising from fasting 85 mg.% to 225 mg.% and 216 mg.% in 3 hours. No sugar appeared in the urine. The carbon dioxide combining power was 23 vol.% and the creatinine 15 mg.%.

Roentgenologic Findings. The skull revealed no evidence of abnormal calcification or increased intracranial pressure. The sella turcica was normal in size and shape without clinoid erosion. No osteoporosis or rarefaction was apparent and the bone age was normal. On the post-axial sides of the right hand and foot rudimentary sixth digits were seen. The abdominal pictures showed kidneys with irregular borders, poorly outlined, and without calculi. There were bifid spinous processes on the second and third sacral segments. A bilateral perirenal air insufflation designed to outline the adrenals revealed nothing striking; however, one of the needles encountered a uriniferous fluid which contained the same nitrogenous constituents as a urine specimen taken two hours later. Because of this fact the operator was led to believe that polycystic kidneys were present. The chest picture showed a moderately enlarged heart of the hypertensive type.

Despite supportive measures the patient's uremia increased and his blood pressure rose to 210/90. At no time while in the hospital did he seem rational, but he would answer when called by name. The mentality was judged to be that of a boy of 12 years, but no psychometric tests were made because of his mental confusion which was predominantly due to his uremia. Because of continued incontinence, urine volume was not measured. He was seen in consultation by the Endocrine Service and a diagnosis of Laurence-Moon-Biedl syndrome was made. Some 21 days after admission he expired in terminal uremia. The final clinical impression was Laurence-Moon-Biedl syndrome, polycystic kidneys with uremia, and bilateral cataracts, probably congenital. Other considerations included hypothyroidism, and renal rickets with secondary hyperparathyroidism.

AUTOPSY

Gross: The autopsy was made 25 minutes after death. Positive findings included a slightly enlarged liver, moderate left ventricular hypertrophy, and a small area of consolidation in the lower lobe of the right lung. The kidneys presented a remarkable appearance; the left weighed 110 gm. and the right 118 gm. Both capsules were firmly adherent, and the parenchyma of each kidney was composed almost entirely of large, dilated, thick-walled cysts which contained clear yellow fluid. There was little normal kidney tissue remaining. Both pelves and ureters were widely dilated. The bladder was distended and hypertrophied (fig. 5). Both prostate and seminal vesicles were infantile, and there was a malformation of the prostatic urethra. There were a series of small elevations of the verumontanum which formed a partial occlusion to the urethra which itself was definitely smaller than normal.

The testes were markedly hypoplastic, 2 cm. in length, and the tubules strung out only moderately well. As described clinically the penis was rudimentary, being but 1 cm. in diameter, 4 cm. in length, and

with the urethral opening just behind the ventral corona. The adrenals, thyroid, parathyroids, and pancreas were grossly normal, and the thymus was atrophic. The cranial cavity revealed no abnormalities and the brain was grossly normal. The pituitary and pineal bodies were normal in size and shape. See figure 6.

Microscopic: Some fat was seen in the muscle fibers of the heart. There was diffuse early pneumonia in the lower lobe of the right lung with some edema, polymorphonuclear infiltration, and a moderate amount of purulent exudate in the alveoli. The bronchial epithelium was eroded. The spleen was moderately congested. In the liver there was extensive cloudy swelling and some fatty change. There was no necrosis or congestion. The gallbladder and gastrointestinal tract were normal.

The kidneys showed extreme scarring and shrinkage of the cortex and medulla. There were few normal glomeruli, and the remaining tubules were markedly dilated. The majority of the tissue was composed of large cysts lined by flattened columnar epithelium with some round-cell infiltration. Vertebral and femur bone marrow showed no abnormalities.

In the testes there was no evidence of maturation of spermatozoa although the germinal epithelium appeared essentially normal with frequent mitotic figures. There was occasional evidence of hyaline degeneration in some tubules. The interstitial cells appeared normal but these were somewhat decreased in number. The cellular structure of the adrenals was normal and a ponceau-fuchsin stain showed no fuchsinophil reaction as described by Broster and Vines (19) in certain cases of adrenogenitalism. The thyroid contained many dilated acini, filled with colloid, and lined with cuboidal epithelium. This was regarded as a typical colloid goiter. The parathyroid glands contained clear principal cells for the most part although a few enlarged water-clear cells were seen. In the pancreas some looseness of the islet tissue was apparent but the gland was otherwise normal. The cellular detail of the pineal body was normal; however, there were several concretions (corpora arenacea) in the pineal stalk next to the pineal recess.

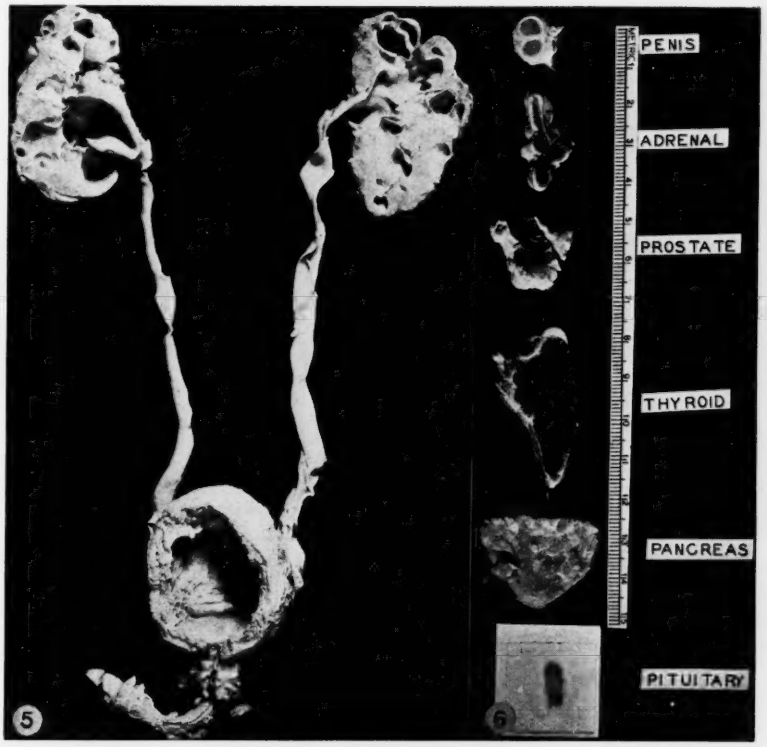

Fig. 5. GENITO-URINARY TRACT OF PATIENT. Note extreme hydronephrosis, hydroureters, and hypertrophy of the bladder. Fig. 6. Comparative scale of various organs.

The pituitary was histologically remarkable. Stained by Kindell's (20) method using eosin-methylene-blue, the anterior lobe was composed chiefly of basophilic and eosinophilic cells. The marked predominance of the basophilic cells colored the sections blue to the naked eye. In serial sections no adenomata were seen. Differential counts by the method of Rasmussen (21) were made on horizontal serial sections. There were 42% basophilic cells, 36% eosinophilic cells, and 22% chromophobes, as compared with the normal counts in the adult male of 11% basophilic cells, 37% eosinophilic cells, and 52% chromophobes according to Rasmussen (21). There was no evidence of any hyalin change in the basophilic cells as described by Crooke (22) in the so-called Cushing syndrome. In the pars intermedia no colloid was seen; however, there was moderate invasion of the posterior lobe by basophilic cells (fig. 7).

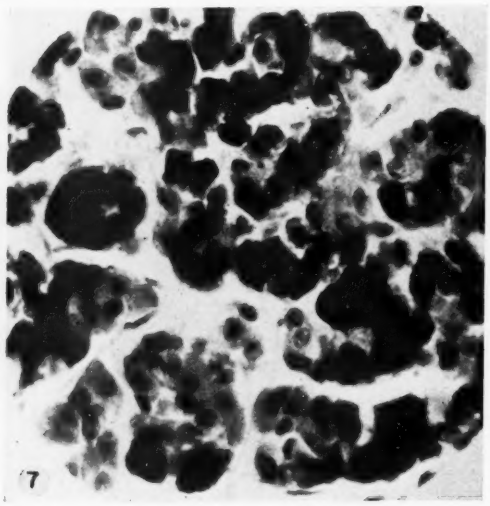

Fig. 7. PHOTOMICROGRAPH OF PITUITARY OF PATIENT. Magnification×400. Note large numbers of basophilic cells.

There were no abnormalities of cellular structure or detail in the cerebral cortex and medulla. Fat stains of various portions of the brain revealed no abnormal fat deposition. There was no atrophy of the gyri; and no hemorrhages, congestion or thrombi of the blood vessels supplying the brain were seen. In areas of the cerebellum there was narrowing of the molecular layer, an absence of Purkinje cells in various places, a slight proliferation of the Bergman cell layer, and a diminution of the nerve cells in the granular layer.

Serial sections of the hypothalamus were taken in coronal plane. The paraventricular nuclei were well outlined and contained the usual multipolar cells with eccentric nuclei and peripheral Nissl substance. Some of the neurons contained more than one nucleus. The supraoptic nuclei were also well outlined with mesial and lateral groups disposed above the optic tract and connected by a few nuclear cells. The neurons in these groups resembled those of the paraventricular nuclei, and no abnormalities were seen. There was perhaps a slight diminution in the number of cells as compared with the normal. The neurons in the tuberal and premamillary nuclei appeared smaller than in the other nuclei and revealed no abnormality. As compared with the normal there appeared to be a reduction in the number of glial cells throughout the hypothalamus.

The blood vessels supplying all portions of the brain revealed no developmental defects of the intima or media. Nowhere were any areas of necrosis or fibrosis seen which might have been ascribed to chronic circulatory insufficiency.

DISCUSSION

In summarizing this case it is apparent that the immediate cause of death was renal failure occasioned by severe bilateral hydronephrosis due to congenital malformations in the lower genito-urinary tract. Although the hypertension may have been due to pituitary or hypothalamic influences, it is more reasonable to assume that the extensive destruction of kidney tissue was responsible. The reversal of the calcium-phosphorus ratio in the blood with secondary parathyroid hyperplasia also may be directly ascribed to renal damage. That there was some abnormality of carbohydrate metabolism is apparent from the patient's decreased glucose tolerance and his extreme obsession and desire for sweets.

It is of interest to note the correlation between this case and the one reported by Griffiths (12) regarding the predominance of basophilic cells in the anterior pituitary. The upper limit of normal variation in basophilic cells of the anterior pituitary is regarded by Rasmussen (21) to be 27%, and in this case they amounted to approximately 42%. In view of the prevailing belief that the hypothalamus is primarily damaged in the Laurence-Moon-Biedl syndrome it is significant to note that 3 of the 6 available post-mortem examinations, have revealed some abnormality in the hypophysis. This does not exclude possible hypothalamic damage, but to date the findings in the hypothalamus have not been remarkable.

The arterial defects in the media as described by Riggs (14) were not seen in our case. Even so it should be remembered that a large percentage of normal brains show medial defects at arterial bifurcations as pointed out by Forbus (23). However, the changes in the cerebellum in our case, particularly the loss of

nerve cells in the granular layer and the diminution of Purkinje cells, might be interpreted as being suggestive of vascular inadequacy according to the belief of Wertham and Wertham (24).

Riggs (14) does not believe that there is a genetic defect in the prosencephalon, but rather that there is evidence of widespread arrest in development in early uterine life. It is her belief that the diencephalic component in the syndrome is in the nature of an abiotrophy, resulting in inadequate functional circulation which in turn is related to the congenital defects in the entire vascular tree. In her cases the picture of diffuse parenchymatous atrophy in the brain is suggestive of chronic circulatory insufficiency.

From a genetic standpoint the explanation of the Laurence-Moon-Biedl syndrome is still not clear. In 1936 Macklin (25) suggested that the syndrome is dependent on two factors involving 2 gene substitutions both of which are necessary before the disease is evident, one of which is dominant and autosomal, the other sex-linked and recessive. Sorsby, Avery, and Cockayne (6) suggest that the syndrome is determined by 2 recessive genes in the same chromosome, or that it is dependent on some chromosomal error such as a dislocation or translocation. Brain (26) also considers the most likely genetic theory to be that the syndrome is inherited as an autosomal recessive, the epiblastic and mesoblastic abnormalities being attributed to 2 separate abnormal genes carried in the same chromosome. Roberts (27) believes that the syndrome is due to a recessive gene, and that more complex explanations are neither necessary nor tenable. He feels that occasional non-expression of recessive genes may occur since there are significantly more males affected than females.

SUMMARY

An additional case of the Laurence-Moon-Biedl syndrome, studied clinically and at autopsy, is reported in detail. The 3 reported autopsies on cases of this syndrome, as well as 2 others kindly supplied by personal communication, are reviewed and discussed.

A significant correlation of this case with one other consists of a striking predominance of basophilic cells in the anterior pituitary.

Hypophyseal abnormalities were noted in 3 of the 6 cases.

The inclusion of the Laurence-Moon-Biedl syndrome within the scope of endocrinology, as well as that of genetics, embryology and neurology is logical, since the cases have always shown some abnormality of the endocrine mechanisms. The genetic responsibility of the production of the syndrome is unquestioned. In this case, in addition to the polydactylism, bilateral cataracts with blindness, possible mental deficiency, bilateral genu valgum, bilateral hydronephrosis, hypospadius, and hypertension, the endocrine implications included marked increase in the basophilic elements of the anterior pituitary, colloid goiter with hypothyroidism, hyperparathyroidism secondary to renal insufficiency, decreased carbohydrate tolerance, obesity, and genital hypoplasia.

It is hoped that future cases of the syndrome which come to autopsy will be studied completely and exhaustively from both the endocrine and neurologic standpoints.

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Cushing's Syndrome

Two Cases Treated with Stilbestrol[1]

[Cushing's Disease]

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This report concerns two patients with Cushing's syndrome who have been observed over a number of years, and in whom administration of stilbestrol appeared to have a significant influence upon the subjective and objective manifestations of the disease.

Case Reports

Case 1. E. R., a white, unmarried female, age 27, was first studied at the Jefferson Hospital in April, 1934. The clinical course to January 1937 has been reported by Bland and Goldstein (1), the chief features of interest being as follows.

Irregularity of the menses, which was the first symptom, appeared in 1933. The periods, which began at the age of 13, had been normal for five years and then became irregular, recurring about every 3 or 4 months. The last period before coming under observation occurred in February 1934. Other prominent symptoms were an increase in weight of 12 pounds in one year (132 pounds), growth of facial hair, extreme dryness of the skin, falling of the hair of the scalp, puffiness of the eyes, marked redness of the face, frequent urination, polydipsia and occasional swelling of the ankles.

Obesity of the face and upper part of the trunk and back were the most striking features on examination. The face was round or 'moonlike' and the skin was tense and of a vivid ruddy hue. There was an abnormal growth of hair on the sides of the face, chin, and upper lip. An acneiform eruption extended from the face to the upper portion of the chest. Several striae were present on the breasts. A fine hair growth was present over the lower abdomen. The external genitalia were normal, the clitoris was not enlarged and pelvic examination was not remarkable.

The blood pressure was 130/80. Roentgenograms showed some 'ballooning' of the sella turcica and thinning of the posterior clinoids. There was no demonstrable decalcification of the spine, pelvis or long bones. Eye-ground examination revealed no significant abnormality. Enlargement of the adrenals could not be demonstrated by intravenous pyelography (Jan. 1935) nor following perirenal insufflation of air (Oct. 1936), the latter study being made by Dr. Harvey Cushing at the New Haven Hospital. The laboratory findings obtained at intervals over a period of 7 years were as follows. The hemoglobin varied from 13 to 17 gm., the R.B.C. from 3.9 to 4.6 millions and the leucocytes from 6,400 to 11,700. The B.M.R. ranged from +9 to −10. The serum cholesterol varied from 188 to 307 mg.%; Ca from 8.7 to 11.2 mg.%; P from 2.5 to 3.3 mg.%; Cl from 531 to 556 mg.%. The phosphatase values were from 6.5 to 8.8 Bodansky units. The total serum protein ranged 6.41 to 6.76 mg.% and the albumin-globulin ratios were normal. Blood urea nitrogen varied from 8.8 to 13.6 mg.%. The urea clearance from 1939 to 1941 ranged from 58 to 70%. The results of the glucose tolerance tests are given in table 1.

Table 1. Glucose tolerance tests in *case 1, E.R.*, cushing's syndrome

	Blood sugar in mg. % after hours								
Date	0[1]	½	1	1½	2	2½	3	4	5	6
4/12/34	118	190		250		250				
3/22/35	69	90		114						
11/ 2/39	68	140		200		206				
10/ 9/40	156		258		306		336	396	330	245
12/12/40	62		111		136		113		78	76
1/ 8/41	75		89		166		106	80		
3/24/41	235		285		392		422	400	326	258
3/31/41	166		306		336		377		285	242

[1] Fasting.

No disturbance of electrolyte balance was demonstrated. Essentially normal values were obtained on several occasions with the test procedure (high Na and Cl and low K intake) described by Cantarow (2) for the detection of cortical hyperfunction (734, 501, and 390 mg.% of urine Cl).

The significant hormone findings are presented in table 2.

During the period from April 1934 to January 1937 the patient received 6 courses of pituitary irradiation with

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some degree of temporary improvement after each course. Following x-ray treatment in June 1936 the plethoric appearance and facial acne almost completely disappeared; there was a marked reduction in hirsutism and a loss of 13 pounds in weight, with decrease in obesity of the trunk. A menstrual period occurred in October 1936. This improved state continued for about one year, but, when seen in February 1938, all previous symptoms had recurred. The weight had increased to 140 pounds and there was marked edema of the face and an increase in 200/160. The patient was confined to bed and given small doses of digitalis for two weeks. Perirenal air insufflation was performed and both adrenals were now found to be enlarged. Because of the patient's poor general condition adrenal exploration was not attempted. Administration of stilbestrol was begun late in November. This had been attempted on several previous occasions, but had had to be discontinued because of nausea and vomiting. By gradually increasing the dosage the patient was now able to tolerate 1 mg. daily and striking improvement occurred

TABLE 2. HORMONE ASSAYS; *Case 1, E.R.*, CUSHING'S SYNDROME

Date Mo./Yr.	Gonadotropins		Estrogens		Androgens[4] Urine/24 hr.	Pregnandiol Urine/24 hr.	Adrenocorticotropic Hormone[5] serum
	Urine/24 hr.	Serum[3]/100 cc.	Urine/24 hr.	Serum[3]/100 cc.			
5/34	Not increased						
1/35			Not increased				
4/39	High, more than 32 I.U.[1]	High, 3 M.U.					
6/39		High, 3 M.U.		High normal, 9 M.U.			
11/39	High, 28 M.U.[1]	High, 3 M.U.	High, 150 M.U.	High normal, 9 M.U.			+++
12/39					Very high, 165 I.U.		
1/40	Low, less than 8 M.U.[2]	Normal		Normal, 3 M.U.	Very high, 180 I.U.		
8/40				Low, less than 3 M.U.			
11/40	Low, less than 8 M.U.[2]			Normal, 132 M.U.		8 mg.	++
12/40				Low, less than 3 M.U.			
1/41					Normal, 60 I.U.	6 mg.	
2/41					Normal 50 I.U.		++

[1] 1 M.U. was the amount necessary to produce corpora hemorrhagia or lutea in ⅔ of infantile mice.
[2] 1 M.U. was the amount necessary to cause 100% increase in uterine weight.
[3] Method of Fluhmann.
[4] Assay by baby chick comb growth method against androsterone, using 3 dosage levels of standard and unknown.
[5] Method described by Jored (3) and Paschkis (4).

hirsutism. Subsequent pituitary irradiation was ineffective.

The patient was admitted to the hospital in May 1939, and again in November, because of increased swelling of the face, headache and pain in one hip. Livid ecchymoses had also appeared on the legs. The blood pressure had increased to 160/120. The breasts had become more pendulous and the striae more marked. There were prominent purplish striae on the lower abdomen also, and increased hair growth in this region. X-ray revealed some demineralization of the skull, but not of the spine. The heart was enlarged. Pituitary irradiation early in 1939 failed to result in improvement. Administration of estradiol, 10,000 R.U. twice weekly for three months produced no beneficial effect other than some improvement in mental attitude due to the occurrence of a menstrual period during the course of treatment.

In September 1940 the patient was readmitted because of marked weakness, increasing hypertension, cardiac decompensation and glycosuria. The blood pressure was promptly. At the end of three weeks the edema of the face and ankles had entirely disappeared, the systolic blood pressure remained below 140 and the glucose tolerance was within normal limits. This marked improvement in the patient's condition continued for a period of three months of unrestricted activity, during which time the dosage of stilbestrol was increased to 2 mg. daily. Growth of hair on the face had regressed, whereas the head hair, which had become very thin and sparse, began to reappear. The finger nails which had been thin, ridged and fissured, returned to normal. During continued administration of stilbestrol, uterine bleeding occurred in December and January. Urine androgen values, which had been consistently high fell to normal levels and the serum adrenocorticotropic hormone concentration (3, 4) which had been excessive on two previous occasions also decreased (table 2).

Late in February the patient noted that her face was again becoming swollen and ruddy and that hair was reappearing on the face. During the following month the

patient lost 10 pounds in weight and became quite weak, and there was a recurrence of the diabetes (fasting blood sugar 235 mg.), which was now more severe than previously and required insulin therapy. There was moderate edema of the face but no evidences of cardiac decompensation. The blood pressure remained at about 160/110. The patient is at present in the hospital. Her general condition has considerably improved. Stilbestrol has been stopped temporarily until the insulin dosage is adjusted.

Case 2. The second patient, *R. K.*, an unmarried female, age 33, was first seen in December 1936. At that time the patient presented the characteristic 'buffalo' type of obesity, swelling of the face, acne, hirsutism and a few abdominal striae, these symptoms appearing gradually over a period of two years. During this interval her dress size had increased from an 11 to a 14, and her weight from 95 pounds to 116 pounds. The menses had been normal until May 1936; one-day flow had occurred in June and July with subsequent amenorrhea.

The blood pressure was 140/90. Glucose tolerance and other laboratory findings were normal. Ophthalmologic examination and x-ray of the sella turcica, spine and abdomen were negative.

Three courses of irradiation of the pituitary and adrenals were given at approximately yearly intervals from March 1937 to March 1939, each being followed by several menstrual periods. The general condition of the patient remained otherwise unchanged. Treatment with large doses of estriol[2] was begun in July 1938 and was at first followed by several menstrual periods. Later, estriol had no demonstrable effects. Facial hair was removed over a period of two years (1938–1940) by electrolysis.

Administration of stilbestrol was begun in June 1940 in a dosage of 0.2 mg. daily by mouth. Menstruation occurred in July. The dosage has been gradually increased to 1.5 mg. daily for the first 3 weeks of each menstrual cycle, and bleeding has recurred on approximately the 28th day of each cycle. No new hair has appeared during the past 6 months, there has been a distinct decrease in the swelling of the face and the patient has noted that she is becoming thinner about the shoulders and upper arms. The blood pressure has ranged from 130/80 to 150/100. Three hormone assays made before the start of treatment with stilbestrol revealed low titers of gonadotropins (less than 8 I.U. per 24 hours), normal estrogen levels (32, 32, and 64 M.U. respectively) and distinctly increased androgen values (90, 135, and 120 I.U. per 24 hours). Androgen values obtained on two occasions since the patient has been on stilbestrol therapy have been within the normal range (60–75 I.U. per 24 hours). Pregnandiol has also been demonstrated (4 and 6 mg.) on two specimens collected in the first week after bleeding. Application of the salt excretion test (Cantarow) yielded results (urine Cl 243 mg.%) which indicated a decreased capacity for excreting Cl in high concentration under the test conditions, suggesting a state of hypercorticoadrenalism.

[2] 2 oz. daily. Emmenin, Ayerst, McKenna and Harrison, Rouses Point, N. Y.

COMMENTS

The value of estrogens in the treatment of Cushing's syndrome is debatable. Good results have been noted by Meyler and Hommes (5), Gill (6), Dunn (7), and others. Albright et al. (8), however, have failed to note any improvement after large doses of natural estrogens. Whether these differences in the response to estrogens are the result of differences in the nature of the underlying pathological processes or in the stage of progress of the disease has not been determined. Moreover, it is not known at the present time whether stilbestrol and the natural estrogens have the same action when given to these patients over a prolonged period of time.

In the first patient administration of stilbestrol was not begun until the condition was far advanced, although estradiol had been given previously for three months with little or no demonstrable effect. The almost immediate improvement in the clinical condition of the patient was striking, especially when viewed in conjunction with such significant objective findings as a marked and persistent reduction in blood pressure, return of the glucose tolerance to normal and reduction in androgen excretion. Equally interesting, however, was the recurrence of certain of the symptoms, particularly the intensification of the diabetes, after three months of continued stilbestrol therapy.

Of interest in this connection are the experiments of Ingle (9) in which diabetes was produced in partially pancreatectomized rats, and to a lesser extent, in normal rats, following stilbestrol administration, results of which have been confirmed by one of us (10).

In the second patient, in whom the disease has been apparently much less severe, the improvement following the administration of stilbestrol has been progressive over a period of a year. The patient has been gratified by an apparent return of normal menstrual function, some loss in weight, some reduction in the obesity of the upper arms and shoulders, and a marked lessening of abnormal hair growth. The improvement with stilbestrol therapy has been much more marked than had been previously obtained with estriol.

The high androgen values in *case 1* and the moderately high values in *case 2* are in disagreement with the findings of Dorfman, Wilson, and Peters (11) and others (12, 13) in patients with 'basophilism.' The former suggested that this may serve as a method of differentiating 'basophilism' from 'corticoadrenalism.' In view of the lack of uniformity in the underlying pathological factors (14) associated with Cushing's syndrome, accurate differentiation on this basis does not seem probable. The consensus of opinion at pres-

ent is that the increased androgen excretion which has been observed in women with masculinizing syndromes in pituitary and adrenal disease is probably of adrenal origin. The chief androgen excreted in these cases seems to be dehydroisoandrosterone (15) which appears to originate from the adrenal cortex also in normal women. The marked reduction in the androgen values following stilbestrol therapy is particularly interesting. One can only conjecture regarding the mechanism underlying this change. Dorfman et al. (11) noted a similar decrease in urinary androgens following administration of theelin in one patient with 'corticoadrenalism,' but believed it to be due to a spontaneous remission or variation since in contrast to the patients reported here, it was not accompanied by evidence of clinical improvement. The presence of pregnandiol in the urine of both of these patients is also of interest, since there is some evidence (16, 17) that this phenomenon, in the absence of a functioning corpus luteum, may be indicative of cortical hyperfunction.

Estrogen studies in both of our patients revealed no significant abnormalities. The concentrations in the serum and urine varied considerably, being usually within the normal range although they were occasionally moderately elevated in *case 1*. High values for gonadotropins, comparable to those of menopausal women, were obtained on several occasions in *case 1* at a time when the disease apparently was progressing rapidly. The significance of this finding is not evident, particularly in view of the fact that the gonadotropins have since fallen to very low levels.

The change observed in the concentration of adrenocorticotropic hormone in the serum is worthy of comment. Before stilbestrol was administered distinctly high values were obtained on two occasions whereas after two months of treatment the concentration was only slightly elevated.

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Pitressin-inhibiting Substance in the Serum of a Patient with Transient Diabetes Insipidus

[Transient Diabetes Insipidus]

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EVIDENCE THAT DIABETES INSIPIDUS is dependent upon a deficiency of secretion by the posterior lobe of the pituitary gland may be summarized as follows: *a*) the symptoms of diabetes insipidus, polyuria and polydipsia, may be relieved by the injection of posterior lobe substance, pitressin; *b*) in animals, diabetes insipidus may be produced by operative removal of or injury to the posterior lobe of the pituitary gland and its connections (1). The rôle of the anterior lobe of the pituitary gland is less clearly understood. However, its presence is essential to the development of experimental diabetes insipidus following the removal of the posterior lobe of the pituitary gland. This is evidenced by the fact that the syndrome of diabetes insipidus does not appear after complete hypophysectomy. Fisher, Ingram and Ransom (1) suggest that the anterior lobe of the pituitary gland may secrete a diuretic hormone which normally is balanced by the anti-diuretic hormone of the posterior lobe of the pituitary gland. If the action of such a diuretic hormone of the anterior pituitary is inadequately opposed, it might be considered to cause diabetes insipidus. Under this concept, diabetes insipidus might be thought to depend upon the relative ratio between the hormones of the anterior and posterior hypophysis, rather than upon the absolute level of either.

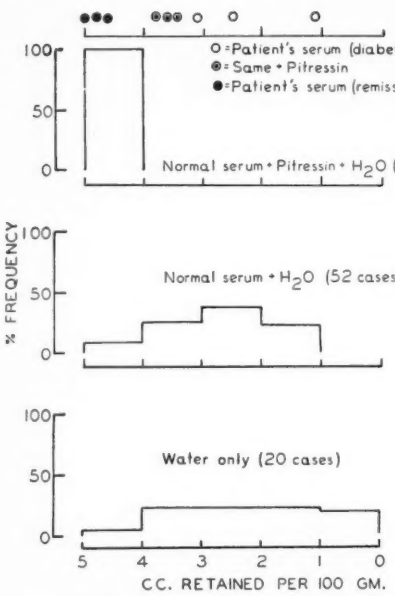

Fig. 1. RESPONSE OF RATS TO PITRESSIN-INHIBITING SUBSTANCE IN SERUM OF PATIENT WITH TRANSIENT DIABETES INSIPIDUS.

During the past two years a patient has been studied who has had periods of diabetes insipidus followed by periods of apparently complete recovery from the syndrome. These recurrences of diabetes insipidus have occurred over a period of many years. This report is from a study of the patient during one phase of diabetes insipidus and during one period of remission.

Technic of measuring anti-diuretic substance in serum. This method has been described previously (2). Normal albino rats are given 5 cc. of water per 100 gm. of body weight by gavage. They are placed in metabolic cages, and the urine passed over a period of 90 minutes is collected and measured. The amount of urine passed is subtracted from the amount of water given the rat, and the difference is expressed in terms of cc. of water retained per 100 gm. of body weight. The frequency distribution of results when water alone is given by this method is shown on the lowest curve in figure 1. The results following injection of normal serum are indicated in the middle curve of the same figure, and they conform, within the limits of individual variation, to the curve for

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[1] Atwater Kent Fellow in Medicine.

water alone. This would suggest that there are not sufficient anti-diuretic factors in normal serum to affect the results of the test. The upper curve indicates the effect of giving normal serum together with an anti-diuretic dose of pitressin[2] (0.12 cc. of a 1:150 dilution of pitressin per 100 gm. of body weight). It will be seen that all animals retained over 4 cc. of water per 100 gm. of body weight.

Case Report

The patient, a 35-year-old woman, had been in reasonably good health prior to 1924 when she developed hyperthyroidism with a basal metabolic rate of +60%. She was treated by sub-total thyroidectomy. The operation was followed by a period of tetany from which she recovered after a parathyroid transplant. Subsequently there were symptoms suggestive of the recurrence of hyperthyroidism for which she was treated by irradiation of the thyroid gland. When she was first seen in this hospital in November 1939, her basal metabolic rate was −6%, and it has remained normal during the period of observation.

Shortly after the sub-total thyroidectomy, the patient developed her first attack of diabetes insipidus. During this period she passed four or five liters of water a day. At times the condition was so severe that she would spend the day drinking large quantities of water while sitting upon the urinal. At the end of about two months the symptoms subsided completely, only to recur a few months later. From that time on these attacks were so numerous that she lost count of them, but estimated that there were three or four similar episodes a year. Certain of these attacks ceased following the injection of pitressin.

The patient has had various ocular complaints which have distressed her since early life. She developed a squint and apparent loss of accommodation in childhood. She has had several attacks of iritis which have not left any visible sequelae. She now has diminished vision in both eyes, marked reduction in dark adaptation and concentric contracture of the visual fields. The ophthalmologists are at a loss to explain the bizarre objective findings; the field changes are not indicative of a pituitary lesion, and there is no evidence of optic atrophy. A complete laboratory examination, including electro-encephalograms and numerous roentgen studies of the skull, have failed to add to the knowledge of the case.

[2] Parke, Davis Company, Detroit, Michigan.

Anti-diuretic Tests

The results of the special anti-diuretic tests with the serum of the patient are charted at the top of figure 1.

a) During a period of diabetes insipidus. Three rats were given 5 cc. of water per 100 gm. of body weight, and 1 cc. each of the patient's serum. They retained 3.3, 2.5, and 1.1 cc. of water per 100 gm. of body weight, respectively. The distribution of results conforms to that of the middle curve of figure 1, and will be seen to be within normal limits.

b) Three rats given the usual amount of water along with 1 cc. of the patient's serum obtained during a period of diabetes insipidus, together with an anti-diuretic dose of pitressin, retained 3.9, 3.6, and 3.5 cc. of water per 100 gm. of body weight. These figures when compared with the top curve of figure 1 exhibit less retention than in similar tests on normal subjects. The change is in the direction of increased water excretion.

c) During a period of remission. Three rats were given the usual amount of water and 1 cc. each of the patient's serum. They retained 5.0, 4.8, and 4.6 cc. of water per 100 gm. of body weight. This, on comparison with the middle curve of figure 1 is seen to be definitely abnormal. Only 2 of 52 animals receiving normal serum retained this much water.

DISCUSSION AND SUMMARY

During the period of diabetes insipidus, the patient's serum contained a substance inhibiting the antidiuretic action of posterior lobe extract. During the period of recovery from the symptoms of diabetes insipidus the patient's serum contained an anti-diuretic factor in excess, with an effect resembling that of pitressin.

The pitressin-inhibiting substance has not been found in the serum of two cases of chronic diabetes insipidus.

This patient has been studied through the kindness of Dr. F. Robb McDonald of the Department of Ophthalmology.

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Extraction and Assay of Lactogenic Hormone in Postpartum Urine[1, 2]

[Lactogenic Hormone]

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THE USE OF LACTOGENIC AND PITUITARY extracts in man and animals for the purpose of increasing the level of milk secretion has been reported by a number of investigators. The reports on the whole have been encouraging, although a few negative results have been obtained in clinical trials. In human hypogalactia, only the lactogenic hormone has been employed, although it seems fairly certain from the animal experiments reported that whole pituitary extracts are more effective than lactogenic hormone alone. This can be attributed to the augmenting effect which these other pituitary hormones are capable of exerting on lactation.

It has been the expressed belief of this laboratory that the lactogenic hormone, which has been shown to be identical with the pigeon crop gland stimulating factor (1, 2) is the hormone concerned specifically with the initiation of lactation. In a recent experiment (3) it was demonstrated that although less lactogen is required to initiate lactation in pseudopregnant rabbits when other pituitary hormones are added, large amounts of pituitary hormones with little lactogen can not initiate lactation. Thus it is clear that while other hormones essential to the body economy may be limiting factors in lactation, these cannot be termed lactogenic hormones.

In cases of deficient lactation it would be highly desirable to be able to assay the relative amounts of the pituitary hormones in the blood and preferably the urine, and thus determine which hormone or hormones are responsible for the deficiency. We have attempted to do this for the lactogenic hormone. The object of this paper is to present our experiences on the extraction and assay of the lactogenic hormone in the urine and to show that a correlation exists between the rate of milk secretion and the lactogenic hormone in the urine. If it can be shown, in cases of hypogalactia, that the lactogenic hormone is not being secreted in adequate amounts, then a good basis would exist for administering this hormone. If there is no deficiency of the lactogenic hormone, and the patient is in good health and receiving adequate nutrition, then other pituitary hormones might be indicated, such as adrenotropin, thyrotropin, the carbohydrate and fat metabolism hormones, or a combination of all these factors.

Lyons and Page (4) were the first to report the presence of lactogen in human postpartum urine. They claimed that at least as much of this hormone is excreted daily as is present in the bovine pituitary. Lyons (5) further showed that lactogen was present in the urine of 4 newborn male and female babies who were secreting 'witches milk.' Hoffmann (6) confirmed this work by assaying the urine of 15 women. No hormone was detected in the urine before parturition in 10 of 11 cases. Following parturition no hormone was demonstrated for the first two days, but beginning on the 3rd day, with the inflow of milk, lactogen could be detected in the urine. Hoffmann (7) further found that in 7 of 8 cases of deficient lactation, the excretion of the lactogenic hormone was considerably less than in the urine of women with ample lactation. Tesauro (8) reported that the injection of untreated or extracted urine from postpartum women gave a definite increase in the crop-gland weight of pigeons. Langecker and Schenk (9) detected lactogen in the urine of women during lactation and also at the end of pregnancy. One and one-half liters of urinary extract was found to be as effective as 1.8 gm. of fresh cattle pituitary. Liard (10) claimed that there was sufficient lactogen in 50 to 150 cc. samples of urine from lactating women to produce milk secretion in guinea pigs primed with large doses of estrogen.

Ehrhardt and Voller (11) assayed the blood and urine for lactogen during the menstrual cycle. They claimed that parallel peaks in both blood and urine were observed at the beginning of menstruation and at the time of ovulation. In addition to these reports, lactogen has also been found in the blood of dairy cattle, goats and rabbits (12); in the serum of mares during pregnancy and lactation (13);

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in mammary tissues and in the colostrum of normal lactating cows (14); in placental tissue (15, 16); and in the liver of man (17), mature cattle and swine (18).

In our own experience we have recovered lactogenic hormone from the urine of normal, menstruating, pregnant and lactating women; normal men; lactating cows; normal, pregnant and lactating goats; also from the blood of normal, pregnant and lactating rabbits; and from the placenta of rabbits that were simultaneously pregnant and lactating. We were unable to find lactogen in the urine of pregnant and lactating rabbits or in fresh liver of mature cows. All these tests were made by the very sensitive 'micro' pigeon test.

MATERIALS AND METHODS

Two methods of treating fresh urine for assay purposes will be described. The first consists of an extraction procedure which results in a dry, stable, water-soluble powder. The second method does not involve chemical treatment; the urine is merely dialyzed, concentrated and injected as such.

Initial attempts were made to precipitate the active principle from the urine with alcohol, acetone, benzoic acid, the hydroxides of iron and aluminum, tungstic acid and tannic acid. Only alcohol and acetone brought about complete precipitation of the active material, although tannic acid also gave positive results. Inasmuch as alcohol was found to be equally or even more effective than acetone, and yet cheaper, alcohol was used to precipitate the active material.

The alcohol precipitation method is a modification of the procedure described by Bates and Riddle (19) for the extraction of lactogenic hormone from pituitary tissue. The steps are as follows: 1) The fresh urine is first filtered through a Buchner funnel with suction. 2) The filtered urine is dialyzed for 24 hours in cold running tap water. For dialyzing as well as for concentrating the urine we use cellulose casing (Visking), ¾ inch in diameter. Several 2-ft. strips are cut, soaked in distilled water for 5 to 10 minutes, tied at one end, filled with 250 cc. portions of urine and tied at the other end. The urine filled casings are put into a four-liter beaker or Erlenmeyer flask, and a continuous flow of tap water is permitted by directing the water to the bottom of the beaker or flask with a piece of rubber tubing. 3) The dialyzed urine is concentrated in the casings by evaporation. This is particularly necessary when large volumes of urine are to be precipitated. The urine-filled casings are suspended from a circular tree and a powerful electric fan is directed on the casings. This should be carried out in a cool room, so that no decomposition will occur. A considerable quantity of water can be evaporated in from 8 to 12 hours, resulting in a 5 to 10 fold concentration of the urine. 4) Two volumes of 95% ethyl alcohol are added to the urine; concentrated NaOH is added a drop at a time until the pH reaches 9 to 10 (phenolphthalein). The precipitate which forms is filtered off with a Buchner funnel using suction. The precipitate is discarded. 5) The pH of the supernatant is reduced to approximately 4 with concentrated HCl, 7 volumes of ethanol are added and the pH is carefully adjusted to 5.4–5.7. 6) The active material is allowed to precipitate overnight in an icebox. 7) The supernatant liquid is separated from the precipitate by centrifuging, and is discarded. 8) The precipitate is washed successively with 95% alcohol, acetone and ether. 9) After the last washing with ether the precipitate can be dried quickly by holding the centrifuge bottle in front of an electric fan for a few minutes and stirring with a glass rod, or else it can be spread out on waxed paper and allowed to dry. The white or grayish white precipitate retains its activity in the dry state for months. It is readily soluble in distilled water. Steps 2, 3 and 4 can be omitted without any loss of hormonal activity; if step 4 is omitted it is necessary to use 9 instead of the 7 volumes of alcohol indicated in 5. However a much purer, water-soluble product can be obtained if the entire procedure is carried out.

TABLE 1. EFFICIENCY OF EXTRACTION METHOD

No. of test	AP hormone added	R.T.[1] of lactogen	Volume of urine	Pigeons used per assay	R.T. U[1] of lactogen recovered	AP hormone recovered
	mg.		*cc.*	*no.*		*%*
1	10	555	200	10	543	97.8
2	10	555	200	10	528	95.1
3	10	555	200	10	534	96.2

[1] Reece-Turner lactogen units. 22.2 R.T. U = 1 I.U. lactogen (22).

The efficiency of the above method of extraction was tested by dissolving three 10 mg. portions of cattle pituitary hormone[3] in three 200 cc. urine samples taken from the same source. Male rabbit urine was used inasmuch as no lactogenic hormone has been found in such urine. This particular pituitary preparation was assayed by the Reece-Turner method (20) and found to contain 555 Reece-Turner units per 10 mg. The three urines were uniformly extracted by the procedure given above (except that dialysis was omitted), and the three resultant precipitates were assayed on 3 groups of 10 pigeons each. The amounts of hormone recovered (table 1) from each of the 3 urines were 543, 528 and 534 Reece-Turner units. This indicates that this extraction method can recover 95% or more of the lactogen in the urine.

The assay of lactogen in the urine of postpartum women indicated that a 'micro' unit response could be obtained with 1 to 10 cc. of urine. Consequently we found it more convenient to use unextracted urine. Like Lyons (21) we tried injecting untreated urine intradermally over the pigeon crop glands, but found that such a severe inflammation resulted that it was difficult to inject the urine quantitatively or to rate the response with accuracy. In addition only a limited amount of urine could be injected

[3] Prepared by Mr. Bergman of this laboratory.

by this means. We improved this method by first dialyzing the fresh filtered urine for 24 hours in cold, running tap water, using cellulose casing. By this step the urine loses much of its toxic and inflammatory properties. The dialyzed urine is then evaporated to at least 1/10th of its original volume by the method described for the extraction procedure above. The concentrated urine can then be assayed immediately, or kept preserved by adding a few drops of hexylresorcinol and freezing it solid. We have kept such urine in the frozen state for as long as 3 months with no obvious decomposition. The advantages of this method are that no chemicals are required for extraction and very little or no inflammation results from the intradermal injections. On the whole we consider this method preferable to the extraction procedure outlined for treating women's postpartum urine.

Table 2. Records of lactating women

Patient	Age, yr.	Weight, lb.	No. of previous pregnancies	Was labor induced? When?	Size of breasts	Wt. of baby at birth, gm.
S	28	154	1	Yes—10 days pre term	Medium	3325
D	21	140	0	Yes—7 days pre term	Medium	3450
L	25	135	1	Yes—past due 5 days	Medium	3550
Gr	24	150	0	Yes—at term	Small	3750
G	21	185	0	No	Large	3650
R	29		5	No	Large	3550
Sch	19	160	0	Yes—at term	Large	3300
Z	37		2	No	Small	3270
F	28	180	0	Yes—at term	Large	3275
C	20	130	0	No	Medium	4380

Table 3. Breast secretion record: daily milk yield in cc.

Patient	Days post-partum											
	1	2	3	4	5	6	7	8	9	10	11	12
S	25	50	233	360	290	470	490	387	410	402	408	466
D			373	390	425	525	338	450	380	408	Allowed to dry	
L	25	118	315	300	450	450	425	500	625	675	600	630
Gr	0	0	117	125	210	174	Allowed to dry					
G	0	261	343	Went home								
R				300	375	475	525	550	Went home			
Sch	25	115	325	Went home								
Z	Insufficient milk—Allowed to dry after 8th day postpartum											
F	Sufficient milk until 11th day											
C	Doubtful sufficiency first 2 weeks postpartum. Stopped nursing by 3rd week.											

For the assay of urinary lactogen we used the very sensitive 'micro' test, which we previously described and compared with other commonly used lactogenic units (2, 22). This 'micro' unit is defined in our laboratory as that amount of hormone which when injected intradermally over the crop glands of 20 common pigeons will elicit a minimum response in $50 \pm 11\%$ of the pigeons. This unit is equivalent to 1/160 I.U. of lactogenic hormone. In all quantitative assays, preliminary tests were made at 2 or 3 dosage levels in a few pigeons in order to approximate the unit. Inasmuch as a pigeon has two crop sacs it is possible to compare two different quantities of the same hormone in the same bird. For example, when injecting the dialyzed urine concentrate, the equivalent of 2 cc. can be injected over the right crop sac and the equivalent of 4 cc. over the left crop sac. If the urine had been concentrated 10 times this would mean that a total volume of 0.2 cc. and 0.4 cc. would be injected over the right and left crop sacs respectively. If it is desired to make the two injection volumes the same, enough distilled water can be added to the smaller dosage to equal the larger volume. Contrary to the report of Bates and Riddle (23), we did not find that differences in injection volume ranging from 0.2 cc. to 1.0 cc. and containing the same amount of hormone caused any significant difference in the 'micro' unit response. We recommend that a number 26 needle, ¾ inch in length, be used for the intradermal injections.

Quantitative assay of women's postpartum urine

Through the cooperation of the nurses in the maternity ward of the University Hospital,[4] the total 24-hour urine output of lactating mothers was

[4] We wish to thank Miss Louise Hilligass, Superintendent of the University Hospitals and the nurses in the maternity ward of Noyes Hospital for their kind cooperation.

collected daily during their confinement. The period of confinement was usually about 2 weeks or less. In addition, urine was collected from one non-hospitalized postpartum patient at weekly intervals. The urine bottles, which contained a little toluene as a preservative, were kept in an icebox during the period of collection. Every day, in the case of the hospitalized patients, the urine was brought to the laboratory and the volume was measured. The urine of each two successive days was combined, and an aliquot portion was extracted. In the case of three patients several hundred cc. of urine were collected before parturition and assayed. Information relative to each patient was supplied on a record sheet. In most cases the daily breast secretion was determined by weighing the babies before and after each nursing. The babies nursed every 4 hours beginning 12 hours after parturition. Although this method does not take into account the residual milk left in the breasts, it serves as a fairly accurate index of the sufficiency of breast secretion.

The 10 patients varied in age from 19 to 37 years and in the number of previous pregnancies from none to 5 (table 2). The breasts were classified as large, medium or small in order to determine whether the size of the breasts was related to the quantity of milk produced, as has been claimed (24). A study of breast secretion by Stewart and Pratt (25) showed that it is possible to predict by the 5th day whether nursing would be adequate or deficient. These authors assumed that a true deficiency of lactation existed when the total yield was less than 250 cc. on the 5th postpartum day. Table 3 shows the relative daily breast secretion of the mothers studied. *Patient Gr* who had no previous pregnancies, and *patient Z* who had two previous pregnancies, were both definite cases of hypogalactia. Nursing was stopped in both cases after the 6th and 8th days postpartum respectively. It is also significant that these two patients had small breasts. *Patient C* who had no previous pregnancies is also considered a probable case of hypogalactia, although nursing was continued for a little over two weeks, after which time it was discontinued because the mother had contracted influenza.

The assay of the urinary lactogen showed considerable variability during the first two weeks after parturition. Excluding *patients Gr, Z* and *C*, there was a range of 653 to 2,000 'micro' units or 4.05 to 12.50 I.U. of lactogenic hormone excreted into the urine daily. From 0.8 cc. to 3 cc. of urine was required to give a unit response during this period. The daily urine volume varied from 765 to 4,020 cc., the volume generally being largest during the first few days postpartum. There was a tendency for the lactogen content of the urine to be higher when the volume of

TABLE 4. ASSAY OF URINARY LACTOGENIC HORMONE

Case	Days p.p.	Urine vol. 24 hr. cc.	cc. urine per micro U	Units per 24 hr. "Micro"	Units per 24 hr. I.U.
S	2–3	2000, 2490	2.0	1127	7.00
	6–7	1720, 1110	2.0	707	4.40
	8	1260	0.8	1575	9.80
			Av.	1136	7.06
D	2–3	985, 1515	2.0	625	3.90
	4–5	2000, 2700	2.0	1175	7.30
	6–7	2110, 2485	2.0	1147	7.15
	8	2120	3.0	706	4.40
	9–10	2090, 2510	3.0	766	4.75
	11–12[1]	1671, 1240	3.0	485	3.00
	13	2245	3.0	749	4.65
			Av.	808	5.02
L	1–2	4020, 2980	2.0	1750	10.40
	3–4	1720, 2500	2.0	1050	6.55
	5–6	3500, 1740	2.0	1310	8.15
	7–8	2040, 2310	2.0	1087	6.75
	9–10	2870, 2075	3.0	824	5.15
	11	1960	3.0	653	4.05
			Av.	1112	6.84
Gr	1–2	1470, 1600	2.0	767	4.75
	3–4	3090, 1240	2.0	1082	6.75
	5–6	3200, 2050	3.0	875	5.45
	7–8[1]	1460, 1780	2.0	810	5.05
	9–10	1115, 1015	2.0	532	3.30
	11–12	1360, 1150	2.0	627	3.90
			Av.	782	4.86
G	1–2	765, 2025	2.0	697	4.35
Sch	1–2	2400	1.5	800	5.00
R	1–2	3940	3.0	656	4.40
	3–8	3010	1.0	1504	9.40
	5–6	4000	1.0	2000	12.50
			Av.	1387	8.76
Z[2]	7–8[1]	1680	5.0	168	1.05
	9–10	2000	6.0	166	1.03
	11	980	6.0	163	1.01
			Av.	166	1.03
F[2]	1		2.5		
	2–3		2.5		
	4–5		1.5		
	6–7		1.0		
	8–9		2.5		
	10–11		2.5		
	12–13		3.0		
C[2]	3–4	2360	2.5	472	2.95
	7	960	3.0	274	1.71
	14–15	1965	7.0	140	.87
	21–22[1]	1360	8.0	85	.53
	28–29	1400	10.0	70	.43
	35–36	1748	10.0	78	.54

[1] Nursing stopped at this time.

[2] These urine samples were only dialyzed, evaporated and injected as such.

urine excreted was greatest. No definite trend is indicated during the first two weeks postpartum; however, this period is only a short part of the normal lactation cycle.

The two cases of definite hypogalactia and the one case of suspected hypogalactia showed lower average titers of lactogenic hormone than the other patients. It is noteworthy in *Gr*, that after nursing was stopped, the urinary content of lactogen dropped from 5.05 I.U. to 3.30–3.90 I.U. *Patient Z* showed the lowest lactogen content in the urine of all the patients studied. Deficient lactation in this case can be definitely correlated with a deficient excretion of the lactogenic hormone into the urine. *Patient C* also showed a low lactogen content during the first two weeks after parturition. After nursing was discontinued in this patient the urinary excretion of lactogen was followed for several weeks thereafter. Lactogenic hormone in the urine fell to about 0.5 I.U. daily, where it remained up to the 5th week postpartum.

The three best lactators, as judged by the quantity of milk produced, *S*, *L* and *R*, excreted, on the average, the highest daily amount of lactogenic hormone.

In the case of the three patients (*L*, *Gr* and *R*) whose pregnancy urine was assayed, the urine definitely contained less lactogen than postpartum urine. Unfortunately it was not possible to secure 24-hour urine samples in these cases, and it was necessary to judge the total amount of lactogen by the volume of urine required for a unit response. From 25 to 50 cc. of urine was required to give a response, which is 8 to 16 times the volume required for a unit response after parturition. The increase in urinary lactogen following parturition is undoubtedly due to the increased activity of the lactogenic hormone of the pituitary.

DISCUSSION

In a previous paper (26) we stated that copious lactation can be initiated only when *a*), there is a well developed mammary gland present and *b*), when there is a high lactogen content in the anterior pituitary. There can be little doubt that many cases of hypogalactia are due to insufficient secretion by the pituitary of the lactogenic hormone, although it is probable that other hormones besides lactogen may be limiting factors in lactation.

Inasmuch as lactogen is the hormone specifically concerned with the initiation of lactation in mammals, it is only natural that this hormone should receive major attention in cases of deficiency. The two simple methods of treating fresh postpartum urine described in this paper, and the availability of a highly sensitive 'micro' pigeon assay technique, should make it possible to determine whether or not the lactogenic hormone is the agent specifically responsible for cases of hypogalactia. If the lactogen content in the urine of such patients is low, then the administration of potent lactogenic extracts might well increase the daily secretion of milk. If the lactogen content in the urine is within a normal range then the administration of other hormones essential for the proper functioning of the body may bring positive results.

Animal experimentation has left little doubt that the administration of whole pituitary extracts is more potent in augmenting milk secretion than lactogenic hormone alone. However, we cannot agree with Folley and Young (27) that other pituitary hormones, such as thyrotropin, adrenotropin or diabetogenic hormones are also lactogenic hormones. We believe these other pituitary hormones are capable of augmenting the activity of the specific pituitary lactogenic hormone solely because of their stimulating effect on the general body organism. This would account for the ability of thyroxine (28–31) or thyrotropin (32) to augment lactation in animals. Work on the effect of thyroxine injections in lactating goats in the declining phase of lactation indicates that the increase in milk secretion is not coincidental with an increase in the lactogen content of the urine (33). On the other hand, thyroxine is known to stimulate the metabolic activities of the body, and this alone could account for the increase in milk production.

The size of the mammary glands is another important factor which must be considered in any attempt to augment lactation. Small glands, with inadequate secretory tissue cannot be expected to respond as well to lactogen as more fully developed mammary glands. In the two cases of definite hypogalactia cited in this paper, it appears more than coincidental that the breasts of both patients were small, although we have no evidence that the breast size affects the secretion of lactogen. Similarly other workers (24) have reported that in women a definite accord exists between the relative size of the two breasts and the quantity of milk produced. It is important, therefore, that nursing should be continued during any attempt to augment lactation since the integrity of both the mammary apparatus and the lactogenic hormone are dependent upon the suckling stimulus (34–37).

SUMMARY

Two methods are described for preparing postpartum urine for the assay of lactogenic hormone. The first consists of an alcohol precipitation, resulting in a recovery of 95% or more of the hormone in a dry, stable, water-soluble form. The second method consists in first dialyzing the fresh urine, then concentrating it by evaporation and injecting it as such. For

the assay of urinary lactogen, the highly sensitive 'micro' pigeon test is used.

The quantitative assay of the urine of 10 lactating women during the first two weeks postpartum revealed a daily range in hormone excretion of from 4.05 to 12.50 I.U. of lactogen. From 0.8 cc. to 3 cc. of urine was required for a unit response in the case of normal lactators. In 3 cases of definite or suspected hypogalactia less lactogenic hormone was found than in mothers with adequate lactation. The 3 best lactators excreted the highest average amounts of lactogen in the urine. Pregnancy urine contained only 1/8th to 1/16th the amount of lactogenic hormone present in postpartum urine.

It is concluded that a very probable relationship exists between the amount of lactogenic hormone excreted into the urine and the level of milk secretion. In cases of true hypogalactia, it is believed that an assay of the urine would reveal whether or not the lactogenic hormone is the factor responsible.

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Growth and Sex Hormones

[Growth]

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IT IS THE PREVALENT OPINION that development of the long bones and growth in general are regulated by the hormones of the anterior lobe of the hypophysis. Hence the gigantic growth in cases of actively secreting tumors of the pituitary, in contrast to the nanosomia observed in the absence of adequate function of the anterior lobe during childhood. The relationship of the thyroid gland is also definitely established. Thyroidectomy inhibits the skeletal development of juvenile animals, while retardation of growth is observed in congenital or childhood hypothyroidism in men. Whether or not a lack of thyroid hormone directly interferes with growth is not quite clear for at least part of the inhibition is attributable to changes in the pituitary followed by a decrease of its growth-promoting function. However, a direct effect of the thyroid on growth is probable, according to clinical experience, because pituitary substitution therapy yields better results if adequate amounts of thyroid are also given.

Evidence of accelerated growth, apparently without contribution of the pituitary, is presented by the syndrome of precocity with macrogenitosomia in children with adrenal cortical tumors. The fatal character of this disease, however, precludes the possibility of long continued observation. Thus, it is impossible to decide whether growth is accentuated only during a limited period of time or is actually increased and of the type that would continue on to real gigantism if the patient were to survive. The advanced ossification suggests rather premature closure of the epiphyseal lines and, hence, limitation of linear growth.

Advanced ossification of the carpal and tarsal centers is noted also in cases of sexual precocity brought about by hormone-producing tumors of the gonads. It is in accord with these findings that Mediterranean and other races whose sexual maturation occurs earlier, are generally shorter of build than later maturing races. Conversely, delayed or inadequate production of sex hormones during childhood or adolescence, accounts for the syndrome of enuchoidism which is characterized by excessive and disproportionate length of the extremities. It seems most likely that the eunuchoid type of growth expresses a state of hyperpituitarism; the lack of epiphyseal closure, even at an advanced age, might be attributed to absence of adequate stimulation by sex hormones although closure of the lines eventually takes place at a later period of life. Persistent hyperpituitarism, after termination of skeletal development, occasionally adds changes of an acromegalic character such as those described in the castrates of the Skopse sect.

Based on these facts, clinical endocrinologists have assumed that epiphyseal closure is brought about by the effect of sex hormones on the growing bones, expressing their full maturation and differentiation. Hence, the use of sex hormones in children or adolescents seems to imply the danger of precipitate ossification, premature closure of the epiphyseal lines and termination of longitudinal growth. This view was put to test by the use of sex hormones for the purpose of terminating, or at least slowing down, excessive growth in cases of hyperpituitarism. Successful hormonal inhibition of pathological growth was reported by Fancher (1) and our own observations confirm his findings. The following case histories illustrate the point in respect to both sexes.

Case 1. D. O., a girl, 9 years of age was seen April 16, 1938 with the complaint of mental retardation. Physical examination was non-contributory. X-rays showed normal skeletal development. Height was 55 in., weight 88 lb. Within the next year she grew 4¼ in. As the height of 59¼ in. was deemed excessive for her age (10 years), estradiol benzoate in 2,000 R.U. doses was given every fifth day. Growth slowed down slightly although the treatment was somewhat irregular. Within the following year a height of 62 in. was reached, an increment of 2¼ in. as compared with 4¼ in. during a similar period of time before the treatment. Weight increased to 114 lb.; the genital organs remained in their infantile state.

On May 27, 1940, oral administration of stilbestrol was started, first with doses of 0.1 mg., later 0.3 mg. daily and subsequently, 1.0 mg. every other day. During the next 3 months the patient grew only one-half of an inch while there was no growth at all in the following 3 months. Subsequently, height increased to 63⅛ in. but remained stationary thereafter until April 25, 1941, when treatment was discontinued. At this time, the epiphyseal lines were

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still widely open; nevertheless, there was no further growth within the next 3 months.

The patient's weight had gradually increased to 124¾ lb. Menstruation started in September 1940 and recurred thereafter as a fairly normal monthly cycle.

Case 2. B. L., a male, 14 years of age, was seen Sept. 17, 1940, with the complaint of abnormally rapid growth, genital hypoplasia and gynecomastia. The genitals were infantile, pubic hair absent and the voice, unchanged. There was considerable enlargement of the mammary glands on both sides, but more so on the right side. Height was 72¾ in. with eunuchoidal elongation of the extremities. Weight was 173 lb.

Testosterone propionate was given twice a week in 25 mg. doses and methyl testosterone, orally, in 10 mg. doses twice a day. Growth was completely arrested during the next 2 months and only one-quarter of an inch was added to his height within 4 months.

Treatment was discontinued after administration of a total of 625 mg. of testosterone propionate with the result of satisfactory genital development, ample pubic hair and masculine voice and demeanor. The gynecomastia disappeared completely on the left side while negligible residues remained palpable on the right side.

Two months after discontinuation of the treatment the patient had grown one-half an inch. Three months later, another ½ in. was added to his height for a total of 1¼ in. for the past 9 months. X-rays at this time showed fairly well advanced closure of the epiphyseal lines, indicating that growth was about to terminate.

In view of the observation that administration of sex hormones in adequate quantity inhibits the anterior lobe of the pituitary and arrests growth in both boys and girls and in view of similar findings in animal experiments (2), it has been considered axiomatic that the use of sex hormones prior to the completion of skeletal development is fraught with danger. McCullagh and McGurl (3) sounded a special warning in describing several cases of eunuchoidism treated with sex hormones in which precipitate closure of the epiphyseal lines was observed. It must be pointed out, however, that these patients were all adults whose epiphyseal lines had remained open well beyond the age period of their physiologic closure. Moreover, the changes produced were obtained with fairly large doses of testosterone. Hence, these observations do not answer the question whether or not closure would occur similarly before the physiologic age period, particularly if smaller amounts of sex hormones were used.

An apparently paradoxical growth-stimulating effect of testosterone was noticed by the writer several years ago and two observations have been previously reported (4, p. 873). The first case was that of a boy, 9 years old, admitted to the Endocrine Clinic of the Gouverneur Hospital with the diagnosis of adiposogenital dystrophy. He received treatment with pituitary extracts, chorionic gonadotropes and thyroid from 1935 until 1938. Testicular development was brought up to normal but the penis remained hypoplastic. Growth in height was also inadequate and had remained stationary for some time. Testosterone propionate in 25 mg. doses was administered over a period of 3 months for a total of 350 mg. During this short period of time the patient suddenly grew one inch in height, concomitant with satisfactory enlargement of the penis and increase in the amount of pubic hair.

The second case was admitted to the Clinic in 1938. He was a boy, 15 years old, though his appearance and genital development was that of a 10-year-old child. Height was 55¾ in. and total growth for the past 4 years was only 2¾ in. Testosterone propionate was given in 25 mg. doses over a period of 6 weeks (total 250 mg.) resulting in satisfactory genital development, definite masculinization and a sudden growth of 1¼ inches.

In spite of these interesting observations, but fearful of untimely closure of the epiphyseal lines, further systematic clinical trials were withheld until our interest was revived by the paper of Rubinstein and Solomon (5). These authors showed that small doses of testosterone stimulated growth, in contrast to the inhibitory effects of larger doses. Similar observations were made by Webster and Hoskins (6) on 8 boys, 9 to 18 years of age who were given testosterone in doses of 75 to 125 mg. weekly. Over a period of 100 days, these patients grew more than twice as fast as before medication or after it was discontinued. Accelerated growth was accompanied by demonstrable retention of nitrogen and phosphorus.

Our present series of cases consists of 7 boys and 3 girls; the former were treated with testosterone propionate, methyl testosterone or both while the latter received diethylstilbestrol. The following is a brief report of these cases.

Case 3. G. S., a male, 13 years of age was seen Oct. 19, 1940; height 57½ in., weight 160¾ lb. Genital development was retarded but not accompanied by eunuchoid proportions of build. Injections of anterior pituitary and chorionic gonadotropins were given for a period of 4 months combined with oral administration of thyroid. There was some improvement of genital development, a weight loss of 16 lb. and growth of ¾ in. in height.

Treatment with testosterone propionate was started Feb. 15, 1940; injections of 25 mg. were given twice a week over a period of 6 weeks. During this short time, the patient grew ¾ in., almost thrice as fast as in the preceding 4 months, while his weight increased 4 lb. in spite of continued diet and thyroid medication.

Case 4. M. P., a male, 14 years of age, was seen June 13, 1940, with the complaint of genital hypoplasia and inadequate growth. Height was 54¾ in., weight 79¾ lb.; general appearance and genital development infantile. X-rays showed widely open epiphyseal lines and retarded

ossification of carpal bones. He had received massive injections of pituitary and pregnancy urine gonadotropins during the past 9 months. He had not grown for the past 12 months.

On June 19, 1940 implantation of the anterior lobe of a calf's pituitary was performed. Within the next 2 months, he grew ¼ in., but the height remained stationary thereafter until October 25 when methyl testosterone was given, in 10 mg. doses, first 3 times a week, then daily and subsequently twice a day.

Record of growth under treatment

Date	*Height, in.*	
6/19/40	54¾	Implantation
8/20/40	55	
10/25/40	55	Methyl testosterone
12/ 1/40	55¼	
1/11/41	55½	10 mg. daily
2/11/41	55¾	
3/10/41	56¼	20 mg. daily
4/25/41	56¾	Added injections of testosterone propionate 25 mg. twice weekly
6/ 1/41	57¼	
6/22/41	57¾	

After 6 months of treatment with methyl testosterone there had been a total growth of 2¾ in. The epiphyseal lines remained widely open in spite of the fact that sexual maturation was complete with ample growth of pubic hair and adequate size of the genital organs.

Case 5. M. G., a male, 15 years of age was seen June 27, 1940, complaining of hypoplastic genital organs, arrested growth and inability to gain weight for the last year. Height was 60¾ in.; weight 88 lb. The patient left for camp without treatment but returned in October, 1940, showing no gain in height or weight. Injection of testosterone propionate was started in doses of 25 mg. twice a week with the addition of methyl testosterone, 10 mg. tablets twice a day. The response was immediate and surprisingly rapid.

Date	*Height, in.*	*Weight, lb.*
10/15/40	60¾	88
11/ 1/40	61½	95
11/19/40	61¾	98
12/13/40	62⅛	100
12/24/40	62½	102
1/27/41	63½	105

During this period of 3½ months, the patient grew 2 in. and gained 17 lb., in contrast to the stationary height and weight during the preceding 16 months. It was interesting to note that incidental interruption of the treatment was always followed by prompt weight loss of 1 to 2 lb.

Case 6. S. M., a male, 12 years of age, with retarded growth and genital development had received treatment with pituitary and chorionic gonadotropins without benefit.

On Jan. 18, 1941, his height was 55 in. and the weight 109 lb. Injections of testosterone propionate, 25 mg., were given twice a week for next 6 weeks, a total of 300 mg. with an increase in height of 1 in. Upon interruption of treatment for the next 6 weeks, no further growth was noted. In view of the adequate genital development, continuation of treatment was not enforced.

Case 7. M. T., a male, 16 years of age, presented the complaint of genital hypoplasia and retardation of growth. He had just finished an 8-month course of treatment with anterior pituitary and chorionic gonadotropins without result. Height was 60¼ in. and weight 118½ lb. Treatment with testosterone propionate, 25 mg., twice a week by injection and methyl testosterone, 10 mg. twice daily by mouth was started Jan. 14, 1941.

After receiving a total of 300 mg. of testosterone propionate within a period of 6 weeks, he grew ¾ of an inch while the weight was 114¾ lb. in spite of strenuous dieting. Four weeks after discontinuation of treatment, another ¼ in. was added to his height while the weight dropped to 109¾ lb. There was no change in height and weight during the next 2 months.

Case 8. H. R., a male, 13 years of age, was seen Feb. 21, 1941 with the complaint of genital hypoplasia and retardation of growth. Height was 57 in., weight 90 lb. After injections of testosterone propionate, 25 mg. twice a week for a period of 6 weeks (a total of 300 mg.), growth of ¾ of an inch was noted with a weight of 91¾ lb. No further growth occurred in the next 4 weeks after discontinuation of treatment while the weight dropped to 90 lb. No further treatment was given in view of the adequate development of the genital organs.

Case 9. S. W., a male, 14 years of age, was seen Jan. 22, 1941, complaining of genital hypoplasia and retarded maturation. He weighed 145 lb.; height was 62¼ in. Growth had been rather slow for the past two years.

Injections of testosterone propionate, 25 mg. twice weekly, during a period of 6 weeks (total 300 mg.) produced considerable improvement of genital development. There was an increment of growth of ½ an inch with 3 lb. increase in weight in spite of thyroid medication and dietary restriction. Except for the latter treatment was discontinued for 2 months with a weight loss of 4 lb. and additional growth of ½ an inch. Upon resumption of injections over another period of 6 weeks, he grew ¾ of an inch for a total of 2 in. during the past 5 months.

Case 10. B. G., female, 12 years of age. This case of infantilism had been treated previously with thyroid and repeated courses of injection with pituitary growth hormone for the past 4 years. On June 17, 1939, her height was 50 in., 3 years behind her age; weight 79½ lb. Thyroid and growth hormone administration was continued for several months. Patient reappeared June 8, 1940 with an added growth of 1¼ in., most of it accomplished during the period of treatment while there was no growth during the past 4 months.

Stilbestrol was given, first 0.1 mg. and subsequently, 0.3 mg. per day; it was taken intermittently and irregularly. During the next 7 months, the patient grew less than 1 in., reaching the height of 52⅛ in. In December, 1940, treatment with stilbestrol was started, 0.5 mg. every other day for the next 3 months, resulting in a growth of ¾ of an inch. Treatment was interrupted for one month due to some incidental illness with no additional growth during that time. Medication was resumed in May and during the next 6 weeks, growth of another ½ in. occurred, for a total of 1¼ in. in the course of 4½ months' treatment with stilbestrol; growth seemed to be more rapid since

the larger doses were given. Menstruation set in on April 4, 1941, and showed a fairly regular cycle thereafter. Yet, there was no growth of pubic hair, nor adequate mammary development. Treatment was continued in view of the still open epiphyseal lines.

Case 11. J. McK., a 7-year-old girl, was seen Dec. 6, 1940, because of retardation of growth and development. Her height was 43¾ in., weight 39 lb., 3 in. and 8 lb., respectively, behind her age. Thyroid, vitamin-B complex and injections of growth hormone were given. There was an increase in weight of 2 lb. but no growth during the next 3 months. On March 15, 1941, treatment with diethylstilbestrol was started, 0.5 mg. every other day. In the course of the next 3 months, she grew 1½ in., as compared with the complete absence of growth in the preceding 3 months. There was no appreciable change in sexual development.

Case 12. A. G., female, 13 years of age. This case of pituitary nanosomia was described in detail in a previous publication (4, p. 367). She was under continuous observation for the past 6 years and received treatment with pituitary extracts and thyroid, for a peroid of 3 years with a net growth of 2½ in. Definite acceleration of growth was observed subsequent to implantation of anterior lobe tissue on April 30, 1938. Height increased from 43¾ to 46 in., an increment of 2¼ in. during a period of 9 months, equivalent to the total growth during the preceding 3 years. Subsequently, however, her growth slowed down to its previous level, amounting to 1¼ in. during the following year, and subsided altogether after attaining a height of 47½ in.

In September, 1940, administration of stilbestrol was started, first, 0.1 mg., later 0.3 mg. daily. In January, 1940, diethylstilbestrol was substituted, 0.5 mg. daily, with the result that she grew 1¾ in. in the course of 8 months, reaching 49¼ in. in June, 1941. The following table shows the changes in height.

Date		*Height, in.*	*Therapy*
April	1935	41¼	pituitary extracts thyroid
April	1938	43¾	implantation
January	1939	46	no therapy
January	1940	47¼	no therapy
September	1940	47½	stilbestrol
			diethylstilbestrol
June	1941	49¾	

Menstruation set in for the first time on April 13, 1941, with regular monthly periods thereafter. Moderate enlargement of the breasts was noted without undue pigmentation of the nipples. There was no growth of pubic hair.

COMMENT

The period of observation in most of these cases is much too short to warrant far reaching conclusions; nor are clinical experiments of this type as well controlled as the usual experimentation on animals. Nevertheless, the prompt response to the administration of sex hormones in all cases and the rather sudden cessation of growth upon discontinuation of therapy speaks clearly for the causal connection between hormonal effects and acceleration of growth. Observations reported by Browne and Ross (7) are fully in accord with our own.

A common feature of all cases reported was the retarded state of genital development. It is possible that sex hormones promote growth only in case of gonad deficiency, making up as it were for the lack of these hormones. Whether or not sex hormones accelerate growth also in case there is no demonstrable need for such substitution therapy remains an open question.

The mechanism of growth stimulation by sex hormones is still obscure, although it would seem that the effects are essentially analogous to those obtained on the genital organs. The precipitate growth of the uterine musculature, the enlargement of penis and clitoris and particularly, the cyclic changes of the endometrium and vagina represent proliferation of cells involving epithelium, muscle tissue and stroma. It is not unreasonable to assume that a substance capable of producing proliferation of cells of such varied histogenesis, actually represents a general growth-stimulating factor, notwithstanding its special affinity to the tissues of the genital organs. Children afflicted with pathological hyperactivity of the adrenal cortex are usually tall of stature which would seem to indicate that other related sterols also share the growth-promoting propensities of the sex hormones. It is remarkable that diethylstilbestrol, the sex effects of which are similar, although the substance is chemically not related to the natural estrogens, also actively stimulates growth.

SUMMARY

Two cases are reported in which sex hormones were successfully used for curbing excessive growth. In a series of 9 male adolescents, retarded growth was accelerated by administration of male sex hormones. Similarly favorable results were obtained in two cases of infantilism and one of nanosomia in female children by administration of stilbestrol.

Testosterone propionate (Oreton), estradiol benzoate (Progynon-B) and methyl testosterone, were supplied by The Schering Corporation, Bloomfield, N. J. Diethylstilbestrol (Estrobene) Ayerst, McKenna and Harrison, Lt'd, Rouses Point, New York.

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EDITORIAL

DIETHYLSTILBESTROL COMMERCIALLY AVAILABLE

THE FOOD and Drug Administration recently has released diethylstilbestrol (4,4′-dihydroxy-α, β-diethylstilbene) into commerce, subject to sale on physicians' prescriptions. This action which was taken after one of the most thorough investigations ever given a pharmaceutical product, prior to its being certified for sale, had indicated beyond any reasonable doubt that the drug possessed no undue toxicity. The medical profession, as a whole, and those clinicians who are keenly interested in the healthy progress of endocrinology, in particular, owe to the Food and Drug Administration a deep debt of gratitude for their services on this occasion.

During the past 3½ years since Dodds and his associates[1] established the estrogenic properties of diethylstilbestrol, much has been written upon the clinical possibilities of this compound. In a recent review in this journal[2] 68 of some 257 reports published before February of this year were summarized. The concensus expressed in this review was that neither had there been established definite toxicity of diethylstilbestrol by studies of liver function, blood and urine chemistry and of blood morphology nor had any seriously untoward symptoms been described following its use. Most of the side effects were described as being temporary. Gastrointestinal disturbances (anorexia, nausea, vomiting and diarrhea) had been reported most frequently; drowsiness, vertigo and dermatoses had also occurred. Some of these untoward symptoms (i.e., gastro-intestinal disturbances) have been related to an induced hyperestrogenism,[3] comparable to that of early pregnancy, rather than to a toxic effect. In general these side effects are more prevalent when large doses are used.

Despite the fact that diethylstilbestrol possesses striking estrogenic properties, it cannot be considered as an ovarian hormone, since it does not contain the cholane nucleus—a common bond between ovarian, testicular and adrenal steroids. Its chief advantages over hormonal estrogens in therapy are its effectiveness by mouth and its cheapness. Diligence on the part of the physician will be necessary to prevent these welcome advantages from becoming therapeutic boomerangs responsible for prolonged and uncritical self-medication.

When powerful pharmacodynamic agents such as diethylstilbestrol are used empirically and contraphysiologically, the sequence of events may be more disturbing than those following the use of tablets of dried ovarian substance. The hormonal estrogens during the past decade have been used uncritically in many instances but relatively little harm has followed because of the small doses employed and the short duration of therapy due to expense and the necessity of parenteral administration. The doses formerly employed may seem almost homeopathic compared with those now possible with diethylstilbestrol. The contraphysiologic use of large doses of this estrogen over long periods of time in dysmenorrhea, 'menstrual migraine' or undesired fertility with the view of overriding normal ovarian cycles, may produce serious damage to ovarian function with associated disturbances in uterine bleeding. In fact, too little attention has been paid, as yet, to the effects of diethylstilbestrol upon the metabolic reciprocities of the hormonal steroids.

The hemostatic effect of diethylstilbestrol upon estrogenic (anovulatory) uterine bleeding should permit a cheaper and more practical regulation of bleeding than was possible with natural estrogens. It should make recourse to the use of androgenic steroids unnecessary. The fact should not be overlooked, however, that the cyclic character of bleeding is not necessarily synonymous with the existence of normal ovarian function. Regardless of its effectiveness in controlling uterine hemorrhage, diethylstilbestrol should not be permitted to mask serious organic pathology, such as fundal carcinoma in the woman with climacteric bleeding.

Over treatment should be guarded against in therapy for gonorrheal vaginitis of childhood, senile vaginitis and undesirable symptoms of the climacteric. Even with hormonal estrogens, these conditions frequently have been overtreated. Prolonged therapy of climacteric women with diethylstilbestrol may lead to troublesome uterine bleeding and serious epithelial responses of the senile endometrium.

Perhaps a striking and practical use of diethylstilbestrol will be in the correction of the cosmetic inelegance of the sexually underdeveloped young woman. Natural estrogens, due to their cost and necessity of parenteral administration, have not permitted any prolonged substitutional therapy for intrinsic hypoövarianism. Now, therapy with diethylstilbestrol for estrogenic failure of the ovaries may produce practically and economically results which are just as satisfactory as those obtained with thyroid substance or insulin in hypofunctional conditions of the thyroid and pancreas. There will continue to exist the obvious limitation that there can be no substitutional therapy for the germinal failure of ovaries of these patients. Peculiar pigmentary responses of the breasts of these patients to diethylstilbestrol have been reported; these are probably similar to the increased pigmentation in the hyperestrogenism of pregnancy.

A caution as to nomenclature seems advisable at this time. The term 'stilbestrol' has been used rather generally

[1] DODDS, E. C., W. LAWSON AND R. L. NOBLE: *Lancet* 1: 1389. 1938.
[2] MORRELL, J. A.: *J. Clinical Endocrinology* 1: 419. 1941.
[3] FREED, S. C.: *J.A.M.A.* 117: 1175. 1941.

instead of diethylstilbestrol, to designate the compound, 4,4′-dihydroxy-α,β-diethylstilbene. This practice may lead to considerable confusion since the Council on Pharmacy and Chemistry of the American Medical Association has followed Dodds and his associates in using *diethylstilbestrol* to describe 4,4′-dihydroxy-α, β-diethylstilbene and *stilbestrol* to designate the less active compound, 4,4′-dihydroxystilbene.

The Food and Drug Administration in releasing diethylstilbestrol has placed a powerful pharmacodynamic principle in the hands of the clinician. He has now full control over its use by his prescriptions. Great diligence should be observed in the determination of its indications and dosage. Empiric and contraphysiologic usages are fraught with serious dangers.

E.C.H.

ASSOCIATION NOTICE

ANNOUNCEMENT OF THE ANNUAL MEETING

THE TWENTY-SIXTH ANNUAL MEETING of the Association for the Study of Internal Secretions will be held in Atlantic City, New Jersey, Monday and Tuesday, June 8th and 9th, 1942. Headquarters will be the Hotel Traymore.

Full directions for submission of titles and abstracts of papers for presentation at the Annual Meeting will appear in the next issue of this Journal.

Abstracts of
CURRENT CLINICAL LITERATURE

Editor: HANS O. HATERIUS. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, ARTHUR GROLLMAN, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. C. PFEIFFER, GEORGE W. THORN, EMMERICH VON HAAM.

GONADS

ZEMKE, E. E., AND W. E. HERRELL.

Bilateral granulosa cell tumors. Successful removal from a child fourteen weeks of age. *Am. J. Obst. & Gynec.* 41: 704. 1941.

The patient, aged 14 weeks, was operated upon in July 1937 for a presumed abdominal malignancy. Solid bilateral ovarian tumors 5 ×5 ×4 and 3 ×2.5 ×2 cm. were encountered and removed. Uterus was normal size. The child recovered and progressed normally. In May 1940, gross and microscopic examination of the ovaries by one of the authors led to establishment of diagnosis. At the present age of the patient (33 months) her health and growth has been normal. The authors regard their case to be that of the youngest patient on record operated upon for granulosa cell tumor.—*E.C.H.*

HYPOPHYSIS

BLAZSO, S., AND V. DUBRAUSKY.

Rôle of the vasopressor and antidiuretic hormone of the posterior lobe of the pituitary gland in the pathogenesis of toxicoses in late pregnancy. *Arch. f. Gynäk.* 170: 651. 1940.

In toxicoses of late pregnancy vasopressor and antidiuretic substances in blood, isolated by the method of Hoffmann and Anselmino and determined by the Burn and Simon method were absent, but they were found in the urine, isolated by the method of Gilman and Goodman and determined by that of Burn and Simon. In some cases of early pregnancy the substances were present. The posterior lobe of the pituitary gland is not of direct importance in the genesis of the toxicosis, but it may react after toxic changes in the organism.—*E. Kaufmann.*

GOECKE, E.

Excretion of anterior pituitary hormone and follicular hormone in urine in Cushing's syndrome. *Arch. f. Gynäk.* 170: 332. 1940.

In 10 cases (8 female and 2 male) no increased excretion of anterior pituitary hormone and follicular hormone was found. Amenorrhea is not a consequence of the increased production of gonadotropic hormone but of its insufficient production.—*E. Kaufmann.*

MURPHY, D. P.

The contractile response of the uterus to posterior pituitary extract during late pregnancy and its relation to the duration of labor. A study of 26 primigravidas with the Lóránd tocograph. *Am. J. Obst. & Gynec.* 42: 281. 1941.

The uterine activity of a consecutive series of 26 primigravidas was registered with a Lóránd tocograph, approximately 19 days prior to onset of labor and while intramuscular injections of posterior pituitary extracts were being given. Individuals who gave positive responses were found subsequently to have shorter labors than those who gave negative responses.—*E.C.H.*

PANCREAS

GREENHOUSE, B.

The newer insulins. *Connecticut State M. J.* 5: 189. 1941.

This is chiefly a brief discussion of the action of the regular, unmodified, soluble amorphous insulin, the newer insoluble protamine Zn insulin and the crystalline insulin. —*Ruth Berggren.*

PARATHYROIDS

JELKE, H.

Über Hyperparathyreoidismus. Ein opperierter Fall mit schweren Merenveräderugen. *Acta med. Scandinav. Suppl.* 114: 1. 1940.

After an extensive review of some 200 cases of osteitis fibrosa cystica described in the literature and a dissertation on the differential diagnosis the author gives details of the case of a 58 yr. old female. The blood Ca was 19 mg.% before operation and fell to 6.5 mg.% after the operation which consisted in the removal of a large multiple adenoma. The kidneys showed marked calculiformation and the bones extensive decalcification with a spontaneous fracture of the right radius and left tibia. The NPN was 71 mg.%. After the operation the NPN rose to 171 mg.% and then gradually fell to practically normal values after a month. Symptoms of tetany appeared and were controlled by Ca gluconate and vitamin D. The bones again became calcified so that X-ray pictures at the end of 2 yrs. were normal—*J.M.L.*